Falls in Parkinson's disease

by

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Contents

Scientific environment

This PhD project was carried out at The Norwegian Centre for Movement Disorders (NKB), Stavanger University Hospital, Norway.

My main supervisor has been Kenn Freddy Pedersen, who is postdoc at NKB and neurologist at the Department of Neurology, Stavanger University Hospital. Kirsten Lode, PhD, at the Department of Research, Stavanger University Hospital and Prof. Jan Petter Larsen, at Network for Medical Sciences, University of Stavanger, have been my co-supervisors. Guido Alves, PhD, who is acting director at NKB and neurologist at the Department of Neurology, and Jörn Schulz, PhD, who is statistician at the Department of Research, Stavanger University Hospital and Department of Electrical Engineering and Computer Science, University of Stavanger, contributed to paper III included in this thesis.

Prof. Ole-Bjørn Tysnes, at the Department of Neurology, Haukeland University Hospital and Department of Clinical Medicine, University of Bergen, contributed to paper III and IV included in this thesis.

Paper IV was carried out in collaboration with Prof. Lynn Rochester, Sue Lord, PhD, and Alan Godfrey, PhD, at Institute for Ageing and Health, Newcastle University, Newcastle upon Tyne, United Kingdom.

During my PhD period, I have been a student of EPINOR, a National Research School of Population Based Epidemiology.

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Abstract

Background

Parkinson's disease (PD) is a slowly progressive neurodegenerative disorder affecting 1% of the population over 60 years. Although motor abnormalities are the core feature of the disease, PD is today considered a multisystem brain disease. While early falls due to impaired balance is considered a red flag for atypical parkinsonism, the frequency of falls at different stages of PD remains uncertain due to methodological limitations in previous studies.

Objectives

The overall aim of this thesis was to describe and achieve a better understanding of the epidemiological aspects of falls in PD across different stages of the disease. To accomplish this, the following objectives were outlined:

- To determine the frequency of falls and demographic and clinical features of falls in 2 population-based cohorts with PD at different stages of disease (paper I).
- To describe the development of falls in a population-based cohort of patients with established PD during 8 years follow-up, and explore risk factors in previous non-falling patients with PD (paper II).
- To describe the development of falls in a population-based incident cohort of patients with newly diagnosed PD vs a matched control group during 7 years of follow-up, and determine concomitants and risk factors of falls in the PD cohort (paper III).
- To objectively examine physical activity levels (time ambulatory, standing and sitting/lying) in a subgroup of PD patients with and without a fall history last 6 months, and identify potential mediators of an active lifestyle (paper IV).

Methods

All included subjects were part of 2 population-based cohorts:

(1) The Stavanger Parkinson project recruited patients with PD between September 1992 and May 1993, initially to determine the prevalence of PD in Rogaland county, Norway. The study was extended with periodically examinations during 12 years. Data from baseline

(n=232), 4-year (n=121) and 8-year (n=64) follow-ups are included in this thesis.

(2) The Norwegian ParkWest study is a multicentre longitudinal cohort study of the incidence, neurobiology and prognosis of PD in Western and Southern Norway. All cases fulfilling strict diagnostic criteria of PD (n=265) were included between November 2004 and September 2006. A cohort of 212 patients with PD was eligible for long-term follow-up. In addition, a total of 201 normal control subjects from the same geographical area were recruited between November 2004 and April 2007. A subgroup of 175 control subjects was matched for age and sex. The participants were monitored closely over 7 years.

Proportions of patients falling at different stages of PD were calculated. Associated features and risk factors of falls were explored, both according to baseline values and longitudinal development. Volume, pattern and variability of physical activity (sedentary behavior, standing and ambulatory activity) were measured by triaxial accelerometers. Selected aspects of physical activity were compared between fallers and non-fallers.

Results

Patients with established PD (mean disease duration 9 years) had a 10-fold higher frequency of falling compared with drug-naïve patients with incident PD. Falling in the established PD cohort was associated with more disability in everyday life (higher UPDRS ADL score) and motor complications (higher UPDRS complication of therapy score).

More than ¼ of newly diagnosed PD patients reported falling at baseline or within the first year of follow-up. The proportion of patients falling increased during the 7-year follow-up, affecting almost ⅔ of all patients. Non-falling patients with incident PD had more than a 3-fold increased risk of falling compared with control subjects during the 7-year study period. Higher age at disease onset and early postural instability and gait difficulty (PIGD) phenotype were associated with increased risk of incident falls.

In patients with established PD, 72% reported falling after 8 years of prospective follow-up (mean disease duration 16 years). Symptoms

representing non-dopaminergic deficiency (higher motor subscore B), higher levodopa equivalent doses and freezing of gait were associated with falls during the first 4 years of follow-up.

In a subgroup of patients from the Norwegian ParkWest cohort (mean disease duration 9 years), those who sustained a fall were more susceptible to being sedentary. Whereas motor impairment (higher UPDRS motor score) was associated with inactivity in non-falling patients, lack of confidence in being able to get up from floor unaided was associated with inactivity in patients with a recent fall history.

Conclusions

Patients with PD fall more often than age- and sex-matched normal controls when newly diagnosed and during longitudinal follow-up. Newly diagnosed patients with PIGD phenotype and higher age may be candidates for specialized assessment and treatment interventions for preventing falls. Patients and caregivers need to be aware of a potential increase in sedentary behavior among patients with PD, especially following a recent fall. Practicing how to get up from floor may be beneficial in patients at risk of falling. The complex heterogeneity of PD and the identification of patients who are moving in and out of a frailty continuum remains a challenge for future research.

List of publications

I. Hiorth YH, Lode K, Larsen JP. Frequencies of falls and associated features at different stages of Parkinson's disease. Eur J Neurol. 2013;20(1):160-6.

II. Hiorth YH, Larsen JP, Lode K, Pedersen KF. Natural history of falls in a population-based cohort of patients with Parkinson's disease: An 8-year prospective study. Parkinsonism Relat Disord. 2014;20(10):1059-64.

III. Hiorth YH, Alves G, Larsen JP, Schulz J, Tysnes OB, Pedersen KF. Long-term risk of falls in an incident Parkinson disease cohort: the Norwegian ParkWest study. Submitted.

IV. Hiorth YH, Larsen JP, Lode K, Tysnes OB, Godfrey A, Lord S, Rochester L, Pedersen KF. Impact of Falls on Physical Activity in People with Parkinson's Disease. J Parkinsons Dis. 2016;6(1):175-82.

List of abbreviations

ADL	Activity of daily living
CI	Confidence interval
FCI	Functional Comorbidity Index
FES-I	Falls Efficacy Scale-International
H&Y	Hoehn and Yahr stage
LED	Levodopa equivalent dose
MADRS	Montgomery and Aasberg Depression Rating Scale
MMSE	Mini-Mental State Examination
NC	Normal control
OR	Odds ratio
PD	Parkinson's disease
PIGD	Postural instability and gait difficulty
RR	Relative risk
UPDRS	Unified Parkinson's Disease Rating Scale

1 Introduction

1.1 General aspects of Parkinson's disease

1.1.1 History

Next year will mark the 200th anniversary of James Parkinson's famous essay on the shaking palsy,[1] in which the characteristic resting tremor, abnormal posture and gait, and clinical course of the condition we now know as Parkinson's disease (PD) was first described. Later the same century, the French physician Jean-Martin Charcot distinguished bradykinesia as a separate feature from rigidity, weakness and tremor.[2] He also proposed the renaming of the disease in honor of James Parkinson.[2] Since then, enormous advances have been made in our understanding of the clinical features (including a range of non-motor symptoms), etiology, pathophysiology, and on the treatments available for patients with PD.

1.1.2 Epidemiology

Parkinson's disease is the second most common neurodegenerative disorder after Alzheimer's disease.[3] Several studies have reported a slightly higher incidence of PD in men than in women, possibly due to potential neuroprotective effects of oestrogens.[4] The annual incidence rates of PD range from 8 to 18 per 100,000 inhabitants.[4] PD is rare before age 50 years,[4] and the highest incident rates are reported in subjects aged 70 to 79 years.[5] The prevalence of PD increases with age, affecting up to 4% in the oldest populations.[4] As PD is related to senescence, the global prevalence of PD is expected to reach about 9 million by 2030 and increasing towards 2050 as the global population ages.[6, 7]

1.1.3 Etiology

The cause of PD still remains unknown in the majority of cases. In fact, the term "idiopathic PD" applies to patients with PD where no definite reason for the disease can be found. Nevertheless, existing knowledge suggests a complex etiology of disease-associated genes and environmental factors in the

pathophysiology of PD.[8] Present knowledge estimates that approximately 10% of PD cases are linked to known gene mutations.[4]

1.1.4 Pathophysiology

The pathology of PD is complex and only partly understood. For long, degeneration of dopamine producing neurons in the pars compacta of the substantia nigra was considered the pathological hallmark of PD. Today, increasing evidence suggests PD to be a multisystem brain disease that also affects several non-dopaminergic transmitter mechanisms. For example, cholinergic pathology in PD seems to be correlated with impaired cognition, gait dysfunction and even falls.[9, 10] Slightly more than a decade ago, Braak and colleagues suggested that pathological changes typical for PD, i.e. presence of intracellular α-synuclein-positive inclusions called Lewy bodies, spread upward from the brainstem to subcortical areas and finally to the cortex.[11] Based on their clinicopathological studies, Braak and colleagues proposed 6 stages of brain pathology, in which motor symptoms become evident in stage 3 (midbrain, including substantia nigra pars compacta). Stages 1 and 2 are considered presymptomatic stages, consistent with reports of olfactory deficits and constipation preceding motor symptoms, whereas stages 5 and 6 (neocortex) are associated with increasing disability and dementia.[12, 13]

Several mechanisms have been implicated in the cause of neuron cell death in PD. These include mitochondrial dysfunction, oxidative stress, excitotoxicity, inflammation and abnormal deposition of misfolded protein aggregates.[14] Each of these factors can potentially contribute to neurodegeneration leading to the characteristic manifestations of PD.[14]

1.1.5 Clinical symptoms

1.1.5.1 Motor symptoms

PD is characterized by parkinsonism, which is a clinical syndrome defined by the presence of bradykinesia in combination with either rest tremor, rigidity,

or both.[15] Early symptoms may be vague and referred to as tiredness, muscular aches and cramps or difficulties repeating sequential tasks such as doing up buttons.[16] A side predominance of motor symptoms is typically observed at symptom onset.[17]

Bradykinesia means slowness of voluntary movement and is characterized by difficulty in initiating and maintaining amplitude or speed of movements. Although secondary features such as rigidity, muscle weakness and tremor may contribute, the main cause seems to be related to insufficient recruitment of muscle force during the initiation of movement.[18] Bradykinesia is often observed as slowness in performing activities of daily living, and is usually assessed having patients perform rapid , repetitive , alternating movements.[19] It is considered the most disabling motor feature in PD, and may present clinically as reduced facial expression, decreased eye blinking, quiet and monotonous speech, impaired finger dexterity and reduced arm swing while walking.[19]

Tremor is the most common and easily recognized motor symptom of PD, affecting 70% to 80% of patients at the time of diagnosis.[20] It is typically present at rest with a frequency of 4-6 Hz, usually involves distal parts of extremity but can also involve lips, chin and jaw. Resting tremor disappears during sleep, is reduced during action, and increases by mental concentration and other stressful situations.[19]

Rigidity is usually detected on examination, whereas patients complain of diffuse or localized stiffness and pain in one limb or the trunk. It is characterized by increased resistance to passive movement of a limb, and presents as “lead-pipe” rigidity (constant resistance in the absence of tremor) or “cogwheel” rigidity (superimposed clicking resistance in the presence of tremor). Subtle rigidity can be elicited by asking the patient to simultaneously perform mirror movements in the opposite limb.[21]

Postural abnormalities in PD are characterized by changes in posture and gait problems with imbalance.[19] Effective integration of sensory information and the generation of appropriate and effective motor responses are essential to maintain upright posture and to initiate corrective responses during walking

or faced with balance perturbations.[22] Impaired regulation of muscle tone, such as axial rigidity and bradykinesia, as well as loss of corrective postural reactions, or righting reflexes, impaired cognitive information processing (i.e. attention and dual tasking) and high occurrence of sensory and visual impairments are considered to have an impact on posture and balance.[22-25] In clinical practice, patients often present with a typical stooped posture with flexion in trunk, hips and knees. The neurological examination usually includes the retropulsion test,[26] which evaluates the ability of patients to recover from a backward pull on the shoulders.

Other motor symptoms

Freezing of gait is a sudden and episodic gait disturbance that usually occurs in more advanced disease. Clinically it is characterized by sudden episodes of inability to produce effective stepping, typically occurring during turning, gait initiation, time pressure and dual tasking or in tight quarters or crowded situations.[27] Although freezing mostly affects the legs, arms and eyelids can also be involved.[19]

Motor complications are reported by more than half of patients during the first 5 years.[28] While the pharmacological management is beneficial in early stages of the disease, the response gradually shortens in most patients over time. As a result, motor fluctuations with relatively immobile "off" periods as well as abnormal involuntary movements (dyskinesias) at peak plasma levels of drugs may develop.[16]

1.1.5.2 Non-motor symptoms

Although PD is defined by the presence of cardinal motor symptoms, most patients will experience non-motor problems across all stages of the disease.[29] These non-motor symptoms are often underreported and may lead to substantially reduced functioning and quality of life.[30] The broad spectrum of non-motor manifestations are shown in Table 1, and includes a wide range of neuropsychiatric problems such as depression and cognitive impairment, sleep disorders, autonomic dysfunction and sensory complaints including pain. [31]

Table 1. The non-motor symptom complex of Parkinson's disease

Neuropsychiatric dysfunction
Mood disorders
Apathy and anhedonia
Frontal executive dysfunction
Dementia and psychosis
Sleep disorders
Sleep fragmentation and insomnia
Rapid eye movement sleep behavior disorder
Periodic limb movement in sleep/Restless legs syndrome
Excessive daytime somnolence
Autonomic dysfunction
Orthostatic hypotension
Urogenital dysfunction
Constipation
Sensory symptoms and pain
Olfactory dysfunction
Abnormal sensations
Pain

Adapted from Poewe.[31]

1.1.6 Diagnosis and differential diagnosis

PD diagnosis is confirmed on autopsy by Lewy body positive neuronal degeneration within the substantia nigra.[21] However, the clinical diagnosis is based on manifestations of cardinal motor symptoms, evaluation of the dopaminergic drug response, and exclusion of other causes of parkinsonism. Still, the earliest parkinsonian symptoms may be subtle at disease onset and misdiagnosis is not uncommon.[15] However, strict diagnostic critera,[15] including evaluation of associated features such as asymmetry of motor symptoms, resting tremor, and good response to levodopa treatment seem to improve the accuracy of the clinical diagnosis of PD and distinguish PD from other parkinsonian disorders. Structural brain imaging, such as magnetic resonance imaging (MRI), may be helpful in distinguishing PD from atypical parkinsonian syndromes such as multiple system atrophy (MSA) and progressive supranuclear palsy (PSP). Functional brain imaging, using dopamine-ligands (DaTSCAN), can also be helpful to eliminate the clinical

diagnosis of PD in uncertain cases (e.g. PD vs essential tremor or drug-induced parkinsonism), but is unreliable when distinguishing PD from atypical neurodegenerative forms of parkinsonism.[21]

1.1.7 Treatment of motor symptoms

Because PD still remains an incurable chronic progressive disease, the overall aim of disease management is to provide symptomatic relief and improve quality of life in patients. In the following, we will address the most common symptomatic treatment options for the motor symptoms of PD, including medications, surgery, therapies and multidisciplinary rehabilitation.

1.1.7.1 Drug treatment

The pharmacological and surgical treatment options from current guidelines[a] in Norway are addressed below.

Levodopa is a precursor to dopamine that passes the blood-brain barrier to replace the dopamine lost by degeneration of striatonigral cells. Levodopa is considered the most effective drug for symptomatic treatment of PD,[32] providing rapid relief of bradykinesia and rigidity associated with pain, and may also improve tremor in many patients. Because long-term levodopa therapy is associated with more frequent motor fluctuations and dyskinesias than other dopaminergic drugs, it is usually the preferred treatment of patients with older age at disease onset.

Dopamine agonists act directly on postsynaptic dopamine receptors.[21] Since dopamine agonists have longer striatal half-life compared with levodopa, they are associated with less rapid development of motor fluctuations and dyskinesias. Dopamine agonists are usually preferred as initial monotherapy

[a] http://www.helse-stavanger.no/no/OmOss/Avdelinger/nasjonalt-kompetansesenter-for-bevegelsesforstyrrelser/Documents/Behandlingsplaner/PSK%20-%20Retningslinjer%20for%20diagnostisering%20og%20behandling%20ved%20Parkinsons%20sykdom.pdf

in younger patients, but may also be given to patients with more advanced disease to enhance treatment effect.

Catechol-O-metyltransferase (COMT) inhibitors delay the peripheral decay of levodopa plasma levels. This longer half-life increases the bioavailability of levodopa and dopamine within the brain.[32]

Monoamine oxidase type B (MAO-B) inhibitors reduce the degradation of dopamine centrally, but have only a mild symptomatic effect on motor function and motor fluctuations. Although MAO-B inhibitors have been suggested to induce neuroprotective effects, results are not yet conclusive.[33]

1.1.7.2 Surgical treatment

In advanced cases of PD, when motor complications or disabling tremor cannot longer be adequately controlled by medications, functional neurosurgery offers a powerful therapeutic alternative. During the last 2 decades, deep brain stimulation (DBS) of the subthalamic nucleus (STN) has become the gold standard neurosurgical treatment for intolerable motor complications in PD. A careful selection of patients is important for optimal surgical outcome: younger age, shorter disease duration, and good levodopa-responsiveness. General contraindications for surgery include severe comorbidities (e.g. cardiovascular problems) or psychiatric problems (depression, psychosis), severe postural instability with frequent falls, and marked cognitive decline.[34]

The use of levodopa in a gel formulation may be suitable for patients who are not candidates for DBS. The gel formulation is delivered continuously via a portable infusion pump through a percutaneous endoscopic gastrostomy tube into the duodenum (Duodopa®), where it is absorbed and produces a steady plasma level.[21]

1.1.7.3 Therapies

The symptomatic non-medical treatment of PD has different individual therapy goals tailored to the disease progression and perceived physical problems. The European Physiotherapy guideline[35] recommends referral to physiotherapist soon after the diagnosis has been established, for self-management advice and education to prevent limitations in functional mobility, to reduce fear of falling, and to improve physical capacity.[35] During later stages, referrals should emphasize specific impairments or limitations such as reduced gait speed. Patients with PD who receive physiotherapy care show improvements in gait, balance, and clinician-rated outcomes such as the Unified PD Rating Scale (UPDRS) when compared to patients with no intervention.[36] However, if withdrawn, physiotherapy is only beneficial in short term (less than 3 months).[36] A possible explanation may be lack of maintenance of strengths and balance. Therefore, regular physical activity of recommended duration, frequency and intensity is especially important in people with PD. Two Cochrane reviews found inadequate evidence from randomized controlled trials to evaluate the effects of occupational therapy [37] and speech therapy [38] in people with PD, although a positive trend was observed.

Multidisciplinary rehabilitation has been implemented in other areas of neurology. For example, care provided in stroke units increases the likelihood to be alive, independent, and living at home 1 year after a stroke.[39] Systematic reviews of multidisciplinary care in PD are scarce,[40-42] and have only included a limited number of randomized controlled trials.[43, 44] Taken together with recent trials,[45-51] these studies show beneficial short term task-specific and dose-dependent responses to the content of the intervention and better quality of life. Delivering the intervention in an inpatient setting may potentially facilitate a higher-intensity program, which may be necessary for patients to reach a physical threshold that enables them to maintain an active lifestyle and lower the drop-out rate.

1.1.8 Clinical course and prognosis

Despite the chronic and progressive nature of PD, motor function and quality of life are usually substantially improved during the first 2-5 years (honeymoon period) after dopaminergic treatment is introduced.[32] However, motor complications and non-motor symptoms not responding well to standard treatment eventually become inevitable in many patients. Nevertheless, prognosis is still highly variable between individuals.

In the longest prospective study of an incident population-representative cohort of PD to date, 46% had developed dementia, 68% had postural instability, and 55% had died by 10 years from diagnosis.[52] Although the standardized mortality ratio was comparable with the general population (1.29), other studies have indicated that life expectancy is still decreased in PD relative to control subjects for those who are older at diagnosis.[21] Furthermore, in the longest running prospective study of newly diagnosed patients with PD (selected cohort recruited for clinical trial), dementia was present in 83% of 20-year survivors, whereas 74% reported hallucinations, 48% symptomatic postural hypotension, 81% freezing, 87% falls, and 35% fractures.[53]

Several risk factors for more rapid functional decline have been identified in patients with PD, including older age at motor onset,[54, 55] cognitive dysfunction,[56] and PD presenting without tremor.[57] Presence of prominent hallucinations is the main risk factor for nursing home placement,[58] whereas dementia seems to be the highest risk factor for shortened life.[59]

2 Falls in the general population

2.1 Definition and classifications

Variations in the definition of fall events may to some extent explain differences in fall rates between similar populations. *Prevention of Falls Network Europe* recommends a fall to be defined as ‘‘an unexpected event in which the participants come to rest on the ground, floor, or lower level”.[60] To minimize recall bias, falls should be recorded using prospective daily recording and a notification system with a minimum of monthly reporting. Telephone or face-to-face interview should be used to rectify missing data and to ascertain further details of falls and injuries.[60] Within a theoretical framework, a fall may also be explained as the consequence of a gap between the interaction of the factors within the individual, a task and the environment.[61] Consequently, walking with slippery shoes on an icy road in low light conditions requires more from the performer compared to walking in-doors in a well-lit environment. Although both task and environment affect the control of movement or the lack of it, the factors within the individual are of special interest in this study.

Fallers may also be classified according to the number of fall events experienced over a defined time period. For example, a recurrent faller is often defined as someone falling more than once during a certain study period. This is an important clarification because people experiencing only 1 fall may be more similar to non-fallers in terms of characteristics than frequent fallers.

2.2 Occurrence, risk factors and consequences

The annual prevalence of falls in community-dwelling populations aged 60 years or older was reported to be approximately 33% in a recent meta-analysis of 10 studies,[62] but prevalence rates vary considerably and increase with age.[63] Women have in general higher fall rates, whereas Japanese populations seem to fall about 50% less when compared to other population-based cohorts.[64] Seasonal variations in falls frequency and deaths from accidental falls are higher during winter months.[64] Particular groups of older people have increased risk of falling. These include subjects with fall history, gait

problems, dependence on walking aids, dizziness, cognitive impairment, antiepileptic drug use, and neurodegenerative disorders such as PD.[65] For example, people with cognitive impairment are 2 to 3 times more likely to fall than age-matched control subjects.[66]

2.3 Prevention

A Cochrane report[67] from 2012 compared intervention for preventing falls with no intervention or an intervention not expected to reduce falls in people aged 60 years or older. Overall, falls were reduced in Tai Chi groups and exercise interventions, usually containing challenging and progressive balance exercise in addition to resistance training. Fall-related fractures were reduced in exercise programs aimed at reducing falls. Interventions designed to improve home safety seem to be effective, especially in people at higher risk of falling and when carried out by occupational therapists.[67] In a meta-analysis by El-Khoury and colleagues, a significant beneficial effect (pooled estimate of rate ratios 0.63) of exercise was found in all categories of injurious falls.[68] The key exercise component in the included studies was balance training.[68] Finally, a meta-analysis of 4 studies showed that multifactorial interventions for preventing falls 6 months or longer significantly reduced the number of recurrent fallers in nursing homes by 21%.[69]

3 Falls in Parkinson's disease

3.1 Epidemiology

Prospective studies of patients with PD have reported fall rates between 35% and 90%.[70] However, these studies were conducted over a short period of time (less than 29 months) and included selected patient samples. Nevertheless, about 1/5 of patients with PD reporting no falls in the previous year seem to experience falling during 3 months of follow-up.[71]

A computerized literature search on MEDLINE, EMBASE, AMED, PsycINFO and CHINAHL was conducted on the 27th of January, 2016. In addition, a manual search was performed to identify potentially relevant publications from a systematic review[70] and a meta- analysis.[71] The following search terms were used: (parkinson*) in title AND (fall*) in abstract, AND ("standardized scoring forms" OR diary OR diaries or calendar* OR log OR questionnaire OR "medical records") in text OR (phone OR call OR telephone OR mail OR card) in text. Abstracts were screened and duplicates, non-observational studies, conference abstracts, studies with number of participants with PD $\leq$ 30, non-prospective studies and articles written in languages other than English were excluded. Finally, 17 studies reporting prospective data on 1 or more falls during follow-up were included.

Figure 1 shows prospective studies using monthly fall diaries alone,[72] combined with regular telephone to verify diaries,[73-86] based on incident reports in nursing homes[87] and finally weekly postcard with telephone follow up.[88] Annual fall rates varied between 31% (Almeida and colleagues) and 90% (Allan and colleagues). One of the main reasons for differences in fall rates is between-cohort heterogeneity. Whereas Almeida and colleagues included 130 patients with PD (mean disease duration 4.9 years) without falling last 12 months or conditions or comorbidities that would affect locomotion or balance, Allan and colleagues included 40 patients (mean age 72 years) with PD dementia (median duration of dementia 2 years).

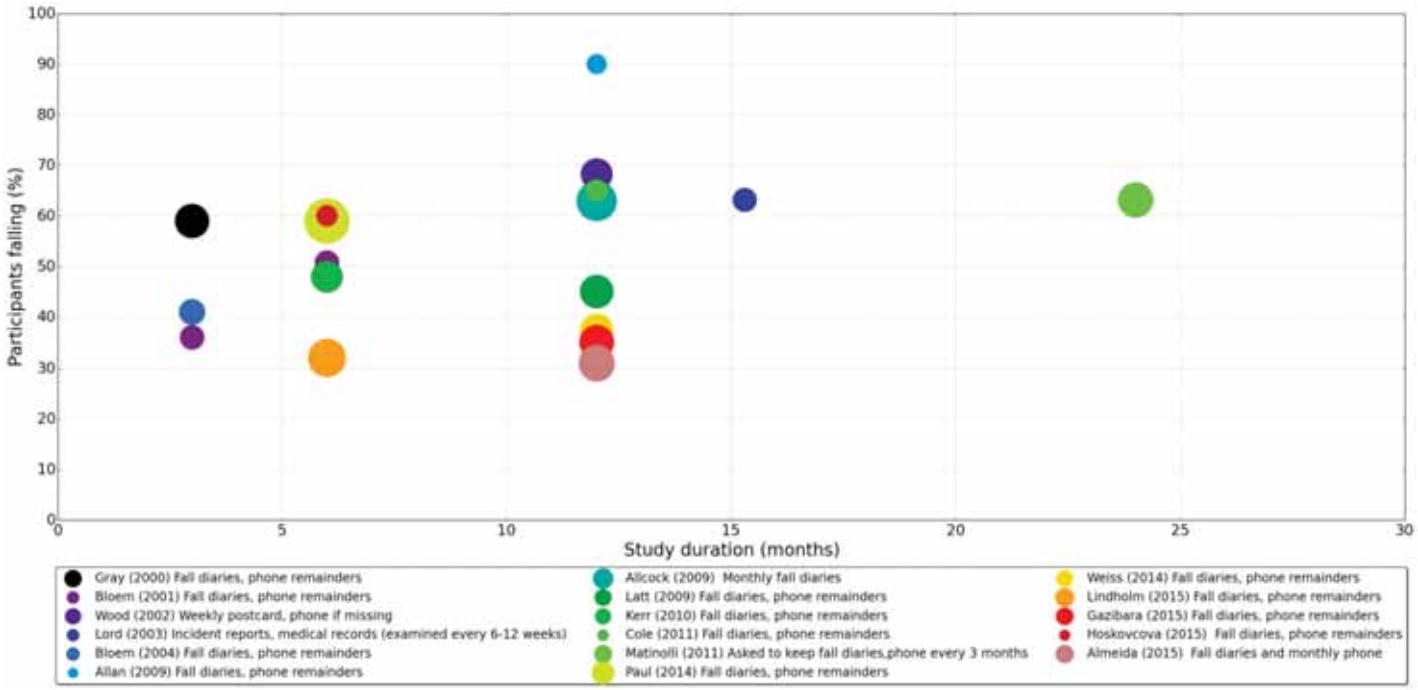

Figure 1. Seventeen prospective studies of falling showing percentage of patients falling according to study duration. Dot sizes correspond to number of patients with PD (range 40-205).

Since both characteristics of the participants and study duration have a major impact on fall prevalence, longitudinal observational studies of incident PD cohorts may probably provide more informative data. In addition, falls may occur sporadically as opposed to regularly. Therefore, longitudinal falls data can detect critical periods in the evolution of falls and their relationship to disease progression and possible amendable falls risk factors. Eventually, randomized controlled clinical trials may be designed to examine preventive interventions covering the most important risk factors.

Prospective population-based studies of patients with incident PD are less common, and the evolution of falls in such cohorts is largely unknown. Figure 2 shows the occurrence of falls in 3 incident studies of PD, including "The Incidence of Cognitive Impairment in Cohorts with Longitudinal Evaluation–PD" (ICICLE-PD)[89] from Newcastle upon Tyne/Gateshead and Cambridgeshire in UK. Between June 2009 and December 2011, a total of 219 patients with PD and 99 age-matched controls were recruited to participate in the ICICLE-PD study. Of these, 111 patients in Newcastle upon Tyne and Gateshead provided data on falls.[90] Information on retrospective falls in the previous year was based on interviews with patients at baseline, and showed that 20.7% had fallen. Thereafter, falls were prospectively recorded monthly using fall diary and a telephone call to verify information and rectify any missing data. During the preceding 12 months, 36.9% of the PD patients reported 1 or more falls. Of the 88 participants without retrospective falls at baseline, 31% had an incident fall during the first year.

Of 208 subjects recruited from a hospital-based movement disorder clinic between 1995 and 2002, 171 Chinese patients with newly diagnosed PD from the Eastern area of Hong Kong Island were evaluated annually for 10 years.[91] Of these, 59% had experienced at least 1 significant fall requiring medical attention. Mean age at disease onset was 62 years and disease duration at the end of follow-up was 11.4 years.

The Sydney Multicentre Study of Parkinson's disease recruited 149 de novo PD patients between 1984 and 1987, who were randomly assigned to

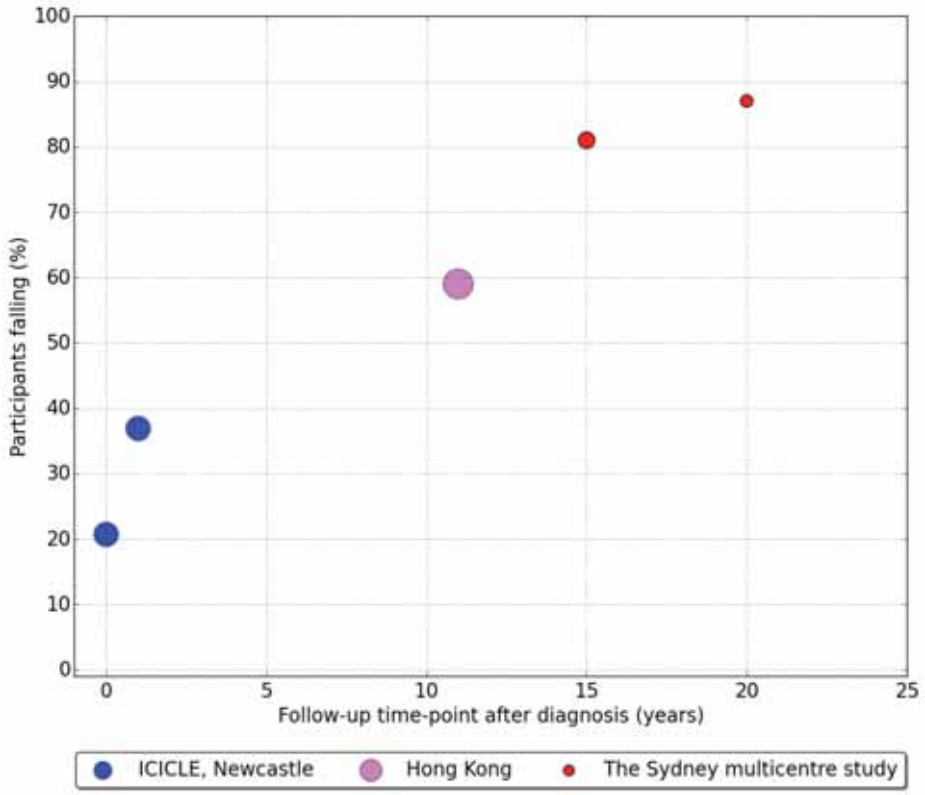

Figure 2. Three incident PD cohort studies reporting falls. Dot sizes correspond to number of participants (range 30-171).

levodopa or dopamine agonist low dose treatment. Of longitudinal assessments performed at 1.5, 3, 5, 10, 15 and 20 years of follow up, the occurrence of falls was only reported at 15 and 20 years. Falls information was collected prospectively as part of the questioning about mobility in activities of daily living, and were recalled since the last visit 5 years ago and recorded as having occurred by the time of the visit they were then attending.[b]

[b] *"The falls were recalled since the last visit and were recorded as having occurred by the time of the visit they were then attending. We did not give patients diaries to fill out. The falls information was collected prospectively as part of the questioning about mobility in activities of daily living. Falls refers to hitting the ground, not merely overbalancing and saving oneself. The information collected was often from both an attending carer and the patient. As many were becoming frail, I think in all or nearly all cases they were with their carer who also helped answer questions."* Mariese Hely, personal communication.

Falls were defined as hitting the ground, not merely overbalancing and saving one self. At 15 years (n=52), falls occurred in 81% of patients and 23% sustained fractures.[92] Five years later (n=30), falls occurred in 87% and 35% sustained fractures.[53] Three additional incident studies of PD, the CamPaIGN study from the county of Cambridgeshire, UK,[52, 93, 94] the NYPUM project in northern Sweden,[95, 96] and the PINE study from Aberdeen[97] have to the best of our knowledge not reported falls data.

3.2 Consequences

Fall-related injuries

A survey study[98] reported that 65% of patients with PD who had at least 1 fall in the past 2 years sustained an injury. Of these, ⅓ sustained a fracture which required surgery in 41% of the cases. Overall, ¾ of all fall-related injuries in this survey study required health care services. Furthermore, a study by Schrag and colleagues showed that the presence of falls within the past 3 months was associated with increased caregiver burden.[99]

Findings from a recent meta-analysis suggest that PD is associated with a 2.7-fold increased risk (95% CI 2.10-3.36) for fracture.[100] Another systematic review and meta-analysis demonstrated a 2.3 (95% CI 1.83-2.83) combined effect size of fracture risk, and reported that PD patients have higher risk of osteoporosis (OR 2.6; 95% CI 1.69- 4.03) compared with healthy controls.[101] In summary, the consequence of increased risk of both falls and osteoporosis seems to be highly associated with the increased fracture risk among patients with PD. Hip fracture in the general population is associated with disability and high admission rate to nursing home.[102] Furthermore, hip fracture patients have a 16% mortality rate within 4 months and 38% within 2 years after surgery.[103] While 1-year mortality rate after surgical treatment of hip fractures was similar between patients with and without PD (22% in both groups), a statistically significant increase in mortality was apparent beyond 2 years.[104] More specifically, the 5-year mortality rate was 90% in patients with PD and 70% in controls.[104]

An autopsy study suggested that frequent falling (remark: a notation in the clinical record that multiple falls were occurring) in advanced PD occur less than 5 years before time of death, regardless of age at disease onset and age at

death.[105] In earlier stages of PD, recurrent falling (remark: falling 2 times or more during a 2-year follow-up period) was not associated with increased risk of mortality 4 years after baseline.[81] Hence, the association between frequent falls and mortality in advanced PD might be a proxy for cumulative frailty in these patients.

Fear of falling

A population-based, prospective, observational study of participants in the Salisbury Eye Evaluation project examined the relationship between falls and fear of falling.[106] Falls in the community dwelling participants (n=2212) aged 65-84 years were an independent predictor of developing fear of falling 20 months later (OR 1.75; P<0.001), and fear of falling at baseline was a predictor of falling at 20 months (OR 1.79; P<0.001). Although this study did not examine patients with PD specifically, the results suggest that individuals who develop one of these outcomes may be at risk for developing the other. Moreover, once falls or fear of falling arise, activities may be limited and thus cause a cumulative frailty that may contribute to increasing fall risk.

In a survey study of 154 PD patients with a mean disease duration of 6 years, the strongest contributing factor to fear of falls was self-rated walking difficulties.[107] In addition, prior falls or near-falls were not independently associated with fear of falling when controlling for other explanatory variables. On the other hand, recurrent falls within a 12-month follow-up period were associated with fear of falls assessed with the activities-specific balance confidence (ABC) scale.[108] These findings highlight the complex relationship between falls, fear of falls and walking difficulties.

3.3 Activity and sedentary behaviors related to falls

Levels of physical activity worldwide are low and decline with increasing age.[109] Patients with PD with a mean disease duration of about 5 years are reported to be 29% physically less active compared with controls (95% CI 10–44%), as measured with a validated physical activity questionnaire.[110] This difference is also evident in patients with incident PD, who produce 30% fewer steps per day compared with controls.[111] In addition, patients with PD walk in bouts of shorter duration and only 3.4% of participants with early PD

and 12.3% of controls achieved the recommended 30 minutes of walking per day comprised of bouts of at least 10 minutes duration (P = 0.02).[111] In contrast, the volume of sedentary behavior was similar in patients with advanced PD compared with controls, although patients with PD were sedentary in bouts of longer duration.[112] Altogether, patients with PD have lower levels of physical activity that are significantly below the recommended public guidelines,[113] potentially leading to severe restrictions in social participation and further deterioration of motor capacities.

Because regular physical activity, including resistance and aerobic training, is particularly valuable in maintaining muscle strength and physical capacity to perform activities of daily living,[114] sufficient dose (i.e. the combination of intensity, duration and frequency) is important.[113] In addition to the disease-associated lower levels of physical activity, other factors might contribute to an overall reduced physical activity in daily life. The relationship between falls and physical activity has at least to some extent been examined in the general older population. People who experience at least 1 injurious fall have lower levels of self-reported physical activity when followed over 3 years.[115] Furthermore, a greater decline in self-reported physical activity was reported while the number of falls increased, and this finding was greater among those who experienced seriously injurious falls.[115] A cross-sectional study of 1680 community-dwelling men aged 71-92 years extended these findings, demonstrating that objectively measured physical activity levels were lower among recurrent fallers than non-fallers.[116]

To our knowledge, only 2 studies have examined selected aspects of objectively measured ambulatory activity in patients with PD related to fall status.[86, 90] Whereas quantity of ambulatory activity was similar in PD patients who had experienced falls compared with non-fallers in both studies, the quality (remark: derived from raw acceleration signal) of gait differed in the study of Weiss and colleges.[86] More specifically, fallers walked with higher step-to-step variability (i.e. larger anterior-posterior width of the dominant frequency), which also proved to predict time to first fall in previous non-falling PD patients using median as a cut-off.[86] Mactier and colleagues on the other hand, reported that falls occurring during changes of posture, such as rising from a chair, were associated with reduced levels of ambulatory activity

compared with non-fallers and patients who reported that falls occurred during everyday walking activities, including stair climbing.[90] Altogether, whereas inactivity and especially injurious falls are correlated in the general older population, the complex relationship between falls and physical activity (i.e. sedentary behavior, standing and ambulatory activity) remains unclear in PD.

3.4 Predicting risk of falling

Clinical prediction models may guide clinicians to identify persons at higher risk of future falls, so that management can be tailored effectively. Fall rates from studies undertaken in community settings show that fall rates in the general population increase with age above 65 years and are higher in older women,[64] suggesting age as one of the key risk factors for falls. This risk may be in part due to physical, sensory, and cognitive changes associated with ageing, in combination with environments that could be better adapted for the aging population. In the following section, factors associated with 1 or more falls in patients with PD are presented, including studies using prospective falls assessment and multivariable risk analyses.

Prospective studies (3-12 months of follow-up) examining risk factors in patients with PD without recent falls have identified disease severity,[71, 73] fear of falling,[71] increased gait variability,[86] postural instability,[79] and poor health related quality of life[84] as potential fall risk factors. Although one study found no between-group differences in postural instability and gait difficulty (PIGD) score,[79] motor phenotypes in PD as risk factors for falling have received little attention.

Previous fall [74, 78, 81, 85, 88] and even near-fall[83] is a consistent and strong predictor (OR ranging between 3 and 42) of future fall in prospective studies. A meta-analysis of 6 prospective studies confirmed that self-report of 2 or more falls in the preceding year yielded a sensitivity of 68% and specificity of 81% when predicting falls over 3 months.[71] A systematic review published in 2013 also reported previous fall as a predictor of recurrent falls.[70]

Disease severity or progression as measured by the UPDRS,[72, 79, 81] Hoehn and Yahr (H&Y) stage,[74] disease duration,[86, 88] and Schwab and England

scale[73] are associated with falls. However, UPDRS motor score was not a significant independent risk factor in 2 other studies. This may be due to shorter disease duration (mean 4.9 years)[73] and an over-fitted model.[86] Interestingly, Bloem and colleagues reported a RR of recurrent falls > 100 for patients who were in H&Y stage 3-4. Pickering and colleagues extended this finding, showing that the risk level increased before reaching a plateau at UPDRS motor scores close to 50, corresponding to a 60% risk of falling within 3 months. Thereafter, a minor reduced risk was observed as the UPDRS motor scores exceeded 50, indicating that the risk of falling decreases in bedridden patients unable to move unassisted.

Freezing of gait is associated with recurrent falls[70] and 1 or more falls in prospective studies.[78, 79, 82] The relationship between freezing of gait and falls was reviewed by Nutt and colleagues. They suggested that the increased risk of falling might result from the associated balance impairments, as these patients show variability in gait metrics between freezing of gait episodes in addition to a markedly reduction in step length, with frequent trembling of the legs during freezing of gait episodes.[117]

Postural instability has been identified as an independent risk factor for falls in PD as measured by postural sway on a firm surface,[79] or a coordinated stability test.[78, 82] In a meta-analysis by Pickering and colleagues, speech, gait and postural instability were the most important "risk items" in the UPDRS motor part after controlling for other UPDRS motor items.[71]

Cognitive impairment defined as Mini-Mental State Examination (MMSE) ≤ 27[78] or MMSE orientation ≤ 9,[82] and dementia[88] are considered independent risk factors for falls in PD. In particular, attentional dysfunction seems to increase the risk of falls in PD, perhaps due to increased distractibility and impaired task switching.[72, 78] Interestingly, a recent pilot study highlighted motor dual-tasking as a potential predictor of falls in PD, although these results still need to be validated in PD patients without fall history.[118]

3.5 Physiotherapy interventions targeted to prevent falls

There is limited evidence for recommending a specific intervention to reduce the frequency of falls in PD.[36, 119] No difference in falls was found between the "intervention" and "no intervention" arm using standard meta-analysis methods.[36] Of 7 included trials in the Cochrane meta-analysis, 1 pilot study reported a significant decrease in fall frequency with 1 hour Tai Chi class twice weekly for 12 consecutive weeks compared with the "no intervention" arm.[120] The European Guidelines for physiotherapy in PD have also noted that evidence to reduce the frequency of falls is limited.[35] Noteworthy, a randomized controlled trial comparing Tai Chi with stretching was included in the guidelines, and showed a difference of 67% fewer falls in favor of Tai Chi.[121]

Two additional clinical trials have explored other forms of exercise with positive findings. Smania and colleagues included patients with PD with H&Y stage 3 to 4 who received intervention for 50 minutes, 3 days a week for 7 consecutive weeks.[122] The experimental group received balance training consisting of exercises aimed at improving both feedforward and feedback postural reactions, and the control group performed exercises not specifically aimed at improving postural reactions (i.e. active joint mobilization and motor coordination exercises). Participants in the experimental balance training group improved postural stability, the level of confidence perceived while performing daily activities, and reduced the frequency of falls. The training effects were maintained for at least 1 month after the end of treatment. A minimally supervised exercise program to improve balance, leg strength, and freezing of gait performed 40 to 60 minutes, 3 times weekly for 6 months did not reduce falls but improved physical and psychological health.[123] However, participants in the exercise group who had less disease severity (UPDRS motor score $\leq$ 26) demonstrated a 69% reduction in falls and a lower proportion of fallers (RR 0.69) compared with the control group.[123] Ultimately, exercise programs targeted to reduce falls, at least 120 minutes weekly for 12-24 weeks may be favorable in early PD, whereas people with more severe disease may instead benefit from a multifactorial, closely supervised intervention.

4 Aims of the study

The overall aim of this thesis was to describe and achieve a better understanding of the epidemiological aspects of falls in PD across different stages of the disease. The specific aims of the 4 papers included were:

- To determine the frequency of falls and demographic and clinical features of falls in 2 population-based cohorts with PD at different stages of disease (paper I).
- To describe the development of falls in a population-based cohort of patients with established PD during 8 years follow-up, and explore risk factors in previous non-falling patients with PD (paper II).
- To describe the development of falls in a population-based incident cohort of patients with newly diagnosed PD vs a matched control group during 7 years of follow-up, and determine concomitants and risk factors of falls in the PD cohort (paper III).
- To objectively examine physical activity levels (time ambulatory, standing and sitting/lying) in a sample of PD patients with and without a fall history last 6 months, and identify potential mediators of an active lifestyle (paper IV).

5 Methods

5.1 Participants and study design

All subjects included in this thesis are part of 2 different patient cohorts and one control cohort recruited from 2 well-defined geographical areas. Both the Stavanger Parkinson project and the Norwegian ParkWest study were approved by the Regional Committee for Medical and Health Research Ethics, Western Norway.

5.1.1 The Stavanger Parkinson project

The Stavanger Parkinson project is a population-based prospective longitudinal cohort study of established PD comprising 9 municipalities with 220,000 inhabitants in Rogaland County, Western Norway. Information from patients attending the only department of neurology in the study area was obtained to identify patients with possible PD.[124] In addition, patient files from Stavanger University Hospital (former Central Hospital of Rogaland), general practitioners, nursing homes, district nurses and information on all members of the PD society in the area were obtained. Nearly 400 participants were examined and interviewed by a neurologist. PD was diagnosed in 245 subjects, of these 239 agreed to participate and were enrolled between September 1992 and May 1993. The diagnoses of idiopathic PD were later changed in 7 patients, leaving 232 patients with definite idiopathic PD at baseline. The patients were prospectively followed up for 12 years, with assessments performed at baseline, 4 years, 8 years and thereafter annually.

5.1.2 The Norwegian ParkWest study

The Norwegian ParkWest study is a multicentre population-based prospective longitudinal cohort study of the incidence, neurobiology and prognosis of PD in Western and Southern Norway. [5] The study area comprises the 4 counties of Sogn and Fjordane, Hordaland, Rogaland and Aust-Agder, with a total population of more than 1 million inhabitants. Recruitment of patients with incident PD in the study area was performed during a 22-month period between November 1, 2004, and August 31, 2006. To achieve total

ascertainment of patients with incident PD, several strategies were applied: 1) handsearching of all referral letters to the participating hospital departments; 2) notification of the study to general practitioners in the study area, other hospital departments and institutions for geriatric care; 3) electronic screening of hospital databases for patients diagnosed with PD within 3 months after study start; 4) an electronic population screening for diagnostic codes for parkinsonism within the largest participating county; and 5) search for antiparkinsonian drug prescriptions.[5] Of 265 patients who fulfilled diagnostic criteria of PD, 212 consented participation in longitudinal study follow-up. During follow up, diagnosis changed or turned uncertain in 19 subjects. A total of 201 normal controls (NCs) were recruited from friends and spouses of patients with PD, or from social clubs for elderly in the same geographical study area. Of the 175 subjects matched for age and sex, 2 were later diagnosed with PD. Study participants were followed prospectively, including clinical evaluation performed by a study neurologist twice annually for patients and every 2 years (except between baseline and 1-year visit) for controls.

5.1.3 Overview of patients and controls

Paper I: Baseline data from the Stavanger Parkinson project (PD = 232) and the Norwegian ParkWest study (PD = 207 and NCs = 175).

Paper II: The Stavanger Parkinson project, including data from baseline (PD = 211), 4-year (PD = 121) and 8-year visit (PD = 64).

Paper III: The Norwegian ParkWest study, including data from baseline (PD = 181 and NCs = 173) until 7 years of follow-up (PD = 142 and NCs = 127).

Paper IV: Data from 48 patients with PD nested within the Norwegian ParkWest study.

5.2 Clinical assessments

5.2.1 Clinical diagnostic PD criteria

Clinical diagnostic criteria for PD differed between studies. In the Stavanger Parkinson project, patients were diagnosed according to the criteria developed by Larsen and colleagues (Table 2).[124]

Table 2. Diagnostic classification according to Larsen and colleagues

	Possible PD	Probable PD, Type A	Probable PD, Type B	Probable PD, Type C	Definite PD
Presence of : **a)** resting tremor **b)** rigidity **c)** postural abnormality **d)** bradykinesia	At least 2 of **a-d**	At least 2 of **a-d**	At least 2 of **a-d**	At least 2 of **a-d**	Presence of **a** and at least 2 of **b-d**
Response to dopaminergic agents	Moderate response	Good to excellent	Good to excellent	Moderate response	Good to excellent
e) Negative CT or MRI	**e**	**e**	**e**	**e**	**e**
f) Dementia or autonomic failure	Mild to moderate **f**	Absence **f**	Presence of mild **f**	Absence **f**	Absence **f**
g) Absence of pyramidal and cerebellar signs and environmental factors	**g**	**g**	**g**	**g**	**g**
h) Unilateral onset and asymmetrical development of disease			**h**	**h**	**h**

In the Norwegian ParkWest study, clinical diagnosis was determined according to Gelb criteria[125] (Table 3-4) and the United Kingdom (UK) PD Society Brain Bank Clinical Diagnostic Criteria[126] (Table 5).

Table 3. Gelb grouping of clinical features according to diagnostic utility

Group A features: characteristic of PD Resting tremor Bradykinesia Rigidity Asymmetric onset.
Group B features: suggestive of alternative diagnoses Features unusual early in the clinical course Prominent postural instability in the first 3 years after onset Freezing phenomena in the first 3 years Hallucinations unrelated to medications in the first 3 years Dementia preceding motor symptoms or in the forst year Supranuclear gaze palsy (other than restriction of upward gaze) or slowing of vertical saccades Severe, symptomatic dysautonomia unrelated to medications Documentation of a condition known to produce parkinsonism and plausibility connected to the patients' symptoms (such as suitably located focal brain lesions or neuroleptic use within the past 6 months)

Table 4. Proposed diagnostic Gelb criteria for PD

Criteria for POSSIBLE diagnosis of PD: At least 2 of the 4 features in Group A are present; and at least 1 of these is tremor or bradykinesia **and** **Either** None of the features in Group B is present **Or** Symptoms have been present for less than 3 years, and none of the features in Group B is present to date **and** **Either** Substantial and sustained response to levodopa or a dopamine agonist has been documented **Or** Patient has not had an adequate trial of levodopa or dopamine agonist
Criteria for PROBABLE diagnosis of PD: At least 3 of the 4 features in Group A are present **and** None of the features in Group B is present (note: symptom duration of at least 3 years is necessary to meet this requirement) **and** Substantial and sustained response to levodopa or a dopamine agonist has been documented
Criteria for DEFINITE diagnosis of PD: All criteria for POSSIBLE PD are met **and** Histopathologic conformation of the diagnosis is obtained at autopsy

Table 5. UK Brain Bank criteria for the diagnosis of PD

Step 1. Diagnosis of a parkinsonian syndrome Bradykinesia (slowness of initiation of voluntary movement with progressive reduction in speed and amplitude of repetitive actions) and at least one of the following: • muscular rigidity • 4-6 Hz rest tremor • postural instability not caused by primary visual, vestibular, cerebellar, or proprioceptive dysfunction.
Step 2. Exclusion criteria for PD • History of repeated strokes with stepwise progression of parkinsonian features • History of repeated head injury • History of definite encephalitis • Oculogyric crises • Neuroleptic treatment at onset of symptoms • More than one affected relative • Sustained remission • Strictly unilateral features after 3 years • Supranuclear gaze palsy • Cerebellar signs • Early severe autonomic involvement • Early severe dementia with disturbances of memory, language, and praxis • Babinski sign • Presence of cerebral tumour or communicating hydrocephalus on CT scan • Negative response to large doses of levodopa (if malabsorption excluded) • MPTP exposure
Step 3. Supportive criteria for PD Three or more required for diagnosis of definite PD: • unilateral onset • rest tremor present • progressive disorder • persistent asymmetry affecting the side of onset most • Excellent response (70-100%) to levodopa • Severe levodopa-induced chorea • Levodopa response for 5 years or more • Clinical course of 10 years or more

5.2.2 Assessment of falls

At all study visits, participants were examined by neurologists experienced in movement disorders. The UPDRS[127] is a standardized examination including questions regarding falling unrelated or related to freezing. Falls were determined according to these items with appropriate cut-offs (highlighted in grey in Table 6).

Table 6. Classification of falls

		Paper 1	Paper 2-4
UPDRS item13: Falling unrelated to freezing	0: None falling unrelated to freezing	Non-falling	Non-falling
	1: Rare falling unrelated to freezing	Rare falling	Falling
	2: Occasionally falls unrelated to freezing. Less than once daily	Falling	
	3: Falls unrelated to freezing an average of once daily		
	4: Falls unrelated to freezing more than once daily		
UPDRS item 14: Freezing when walking	0: None freezing when walking		
	1: Rare freezing when walking		
	2: Occasional freezing when walking		
	3: Occasionally falls from freezing		Falling
	4: Frequent falls from freezing		

Fear of falling during social and daily activities, inside and outside the home, was measured using the 16-item questionnaire Falls Efficacy Scale-International (FES-I).[128]

5.2.3 Assessment of motor symptoms

The Hoehn and Yahr scale[17] describes the progression of motor symptoms from stage 0 (no visible symptoms of PD) to stage 5 (bilateral parkinsonism and bedridden unless aided). Progression in H&Y stages correlates with standard PD rating scales like the UPDRS, deterioration in quality of life, and neuroimaging studies of dopaminergic loss.[129]

The Schwab and England scale[130] assess the overall functional independence in terms of daily activities, and ranges on an 11-point scale from 100% (completely independent, unaware of any difficulty) to 0% (completely bedridden, vegetative dysfunction).

The UPDRS[127] is the most commonly used assessment instrument to monitor the longitudinal course of PD. It comprises 4 sections with a max total score of 199 points that reflects disease severity. Part I evaluates mentation, behavior, and mood (range 0-16 points). Part II examines activities of daily living (ADLs), such as speech, salivation, swallowing, handwriting, cutting

food, dressing, hygiene, turning in bed, falling, freezing when walking, walking, tremor and sensory complaints (range 0-52 points). Part III is a clinician-rated motor examination (range 0-108 points). Part IV includes information about complications of therapy last week (range 0-23 points).

Jankovic and colleagues derived 3 PD subtypes by using the ADL and motor parts of the UPDRS to calculate the ratio of mean tremor score/ mean PIGD score. Subjects with a ratio of less than or equal to 1.0 were defined to have a PIGD phenotype, those with a ratio greater or equal to 1.5 a tremor phenotype, and those with a ratio between 1.0 and 1.5 were specified as an indeterminate phenotype.[20]

In paper II, the UPDRS motor section was used to define 2 subscores that represented predominantly dopaminergic deficiency (subscore A: facial expression, tremor, rigidity, and bradykinesia; range 0-80) and non-dopaminergic deficiency (subscore B: speech, arising from chair, posture, gait and postural instability; range 0-20).[131]

Freezing of gait *unrelated* to falls was defined as a score 1 or 2 on UPDRS item 14.

Dyskinesias were defined as a score ≥ 1 on UPDRS item 32 in paper II.

In paper II, comorbidities were measured according to the Functional Comorbidity Index (FCI).[132] The FCI (range 0–18), is an 18-item list of diagnosis developed with physical function (SF-36 physical function subscale) as the primary outcome. The FCI scores were determined according to ICD-10 codes described in a paper by Gabbe and colleagues.[133]

5.2.4 Assessment of non-motor symptoms

Depressive symptoms were evaluated with the Montgomery and Aasberg Depression Rating Scale (MADRS),[134] which consists of 10 items completed during a clinical interview. Each item has a defined scale step (range 0-6). A cut-off score of 17/18 indicates major depression with high specificity in patients with PD.[135]

Global cognitive function was examined using the Mini-Mental State Examination (MMSE).[136] MMSE is a 20-item questionnaire assessing orientation, registration, attention and calculation, recall, language and copying (range 0-30).

Dementia associated with PD (PDD) was diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised[137] in the Stavanger Parkinson project, whereas the more recently proposed consensus criteria for PDD[138] were applied in the Norwegian Park West study.

5.2.5 Assessment of physical activity

Photo: Ylva Hivand Hiorth

We used the validated accelerometer activPAL3™ (PAL Technologies Ltd., Glasgow, UK) to objectively quantify free-living sedentary, upright and ambulatory activities.[139, 140] The activPAL3™ is a small (35 x 53 x 7 mm) and lightweight (15 g) device with a sampling frequency of one reading of acceleration every 1/20th of a second. Once programmed for 7 days of wearing time, the device was applied a waterproof attachment (nitrile sleeve for activPAL3™ and 3M Tegaderm transparent dressing) and attached on the mid-line of the thigh least affected by parkinsonism, in the lower part of femur positioned one third of the way between hip and knee. Participants were instructed to remove the device only during bathing, and were provided with replacement dressing to re-attach the device if necessary. Upon completion of recording, the device was removed in the clinic or posted back to the researcher as convenient for the participants.

The following outcomes from the activPAL data were computed: *(1)* Volume: percentage of time and total number of sedentary, standing and ambulatory bouts per week. *(2)* Pattern (alpha, α): a unit-less parameter which is derived from a power distribution of bouts of activity, where a lower α for ambulatory behavior indicates a distribution derived from greater proportion of long bouts.[141] *(3)* Variability: the within subject variability (seconds) of bout

length was calculated using a maximum likelihood technique due to a log-normal distribution, where a high variability figure indicates a more varied length of bout.[142] *(4)* The lengths of bouts by strides in 3 different durations were identified in a period of 7 days and described as total number of strides occurring in bouts of low duration (<10 strides), medium duration (10 -50 strides) and long duration (>50 strides).[143]

5.3 Statistical analysis

Descriptive statistics: Mean, standard deviation, number and percentage of participants falling and characteristics were calculated to describe the study cohorts. In paper III, relative risks (RRs) with 95% confidence intervals (CIs) were calculated for falling during the 7-year follow up. Due to non-normality distribution and a rather small sample size in paper IV, median and range were reported instead of mean and standard deviation.

Comparison of groups: Differences in clinical features between non-fallers and fallers were calculated using Spearman's rank correlation (paper I) and Mann-Whitney tests (paper II-IV). Differences in proportions of categorical variables were analyzed by Chi-Square tests or Fisher's exact tests where appropriate. In paper III, overall non-falling survival curves were estimated by the Kaplan–Meier method to determine time to first fall.

Regression models: Logistic regression analyses with falling or non-falling as the dependent variable were used to explore features associated with falling and risk factors of falling in paper I and II. Odds ratios (ORs) were presented with 95% CIs. Model fit and usefulness were tested with the Hosmer and Lemeshow Test and the Nagelkerke R Square, respectively. Univariate variables associated with future falls with a p value <0.05 were included in the multivariable regression analyses. In paper IV, standard linear regressions were used to study explanatory variables that contributed significantly to total time spent sedentary, standing, and ambulatory by calculating adjusted explained variance (R^2) and standardized coefficients (β). Univariate linear regression was conducted initially, with variables with a p value <0.05 entered into the multivariable models. This cut-off may be considered a bit conservative, but was chosen in order to avoid overfitting. Due to the high intercorrelation between UPDRS motor score and H&Y stage, the variable

with the highest standardized β value was entered into the multivariate linear regression analysis. The ratio of cases to independent variables in the linear regression analyses was evaluated using $N \geq 20 + 5m$ (where m is the number of independent variables) in the multivariate models.[144]

Regression models for repeated data: In paper III, marginal population-level estimates obtained by generalized estimating equations (GEE) were applied to explore concomitant features of falls (association model) and investigate risk factors for incident falls (risk model). The association model was based on all patients in the cohort, with presence or absence of falls as dependent variable. In the risk model, drug-naïve patients at baseline without falls were first included. Next, we included patients at 1-year follow-up without previous falls and added dopaminergic treatment as an independent variable to our model. Dependent variable in the risk model was incident falls (yes or no). In both models, the following independent variables were examined at each study visit: sex, age and disease duration at baseline, UPDRS motor score, freezing of gait (yes or no), PIGD phenotype (yes or no), body mass index (BMI), MADRS score, MMSE score, levodopa equivalent dose (LED) and follow-up time. Because of missing data by design, we used a multiple imputation then deletion procedure, as described by Hippel.[145] An autocorrelation structure was chosen for the working correlation matrix. As the dependent variable (fall status) was binary, the mean was related to the covariates by the logit link function. GEE analyses were first conducted with all variables evaluated separately (unadjusted model), then combined (adjusted model), and finally by removing variables with the highest p value in the adjusted model using a stepwise backward selection procedure (final model).

All analyses were done using SPSS-software.

6 Results

6.1 Paper I

We found a 10-fold higher frequency of fallers in the cross-sectional cohort with established PD compared with the cohort of drug-naïve incident PD. The proportion of fallers at different stages of PD (both cohorts) as measured with H&Y increased with disease progression, as shown in Figure 3 below.

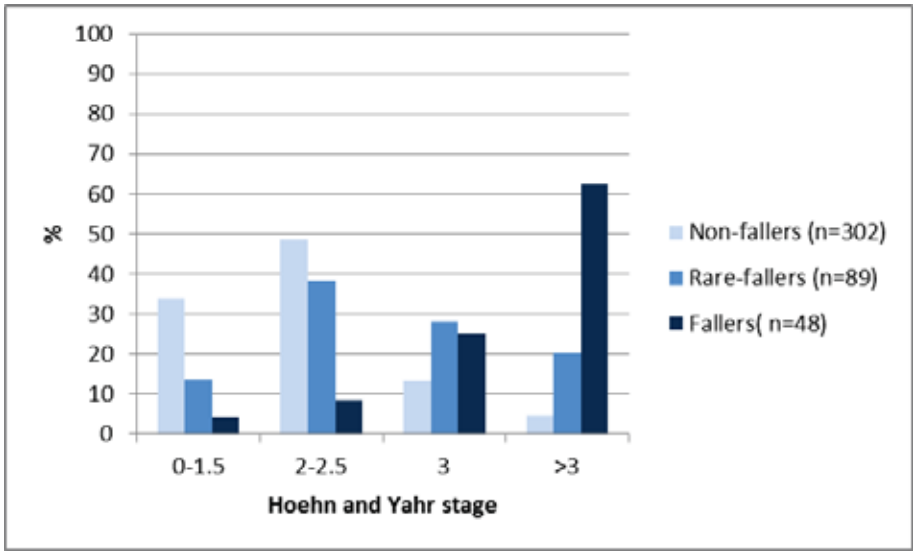

Figure 3. Frequency of falls at different stages of PD.

All fallers in both study populations were classified as having PIGD or indeterminate motor phenotype. The distribution of motor phenotypes among non-fallers, rare-fallers and fallers are shown in Figure 4.

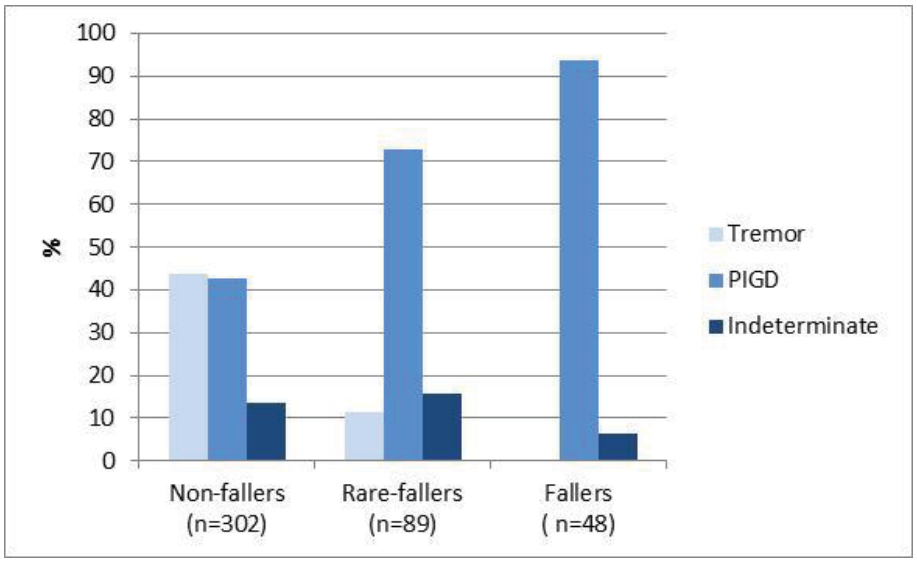

Figure 4. Frequency of falls according to motor phenotypes.

Higher scores on UPDRS ADL and more motor complications (UPDRS complication of therapy score) were associated features of falling in the cross-sectional cohort.

6.2 Paper II

Figure 5 shows that the occurrence of fallers increased from 41% at baseline to 72% in the remaining patients after 8 years of follow-up. Among the 124 non-falling patients at baseline, 38% changed fall status within first 4 years, whereas 40% of non-falling patients at the 4-year visit reported falling between the 4 and 8 years follow-up. Among the 124 non-falling patients at baseline, sporadic freezing of gait was a strong independent risk factor of falls during the first 4 years of follow up, corresponding to an OR of 6.6. In addition, higher LED and motor subscore B were independent risk factors of falls.

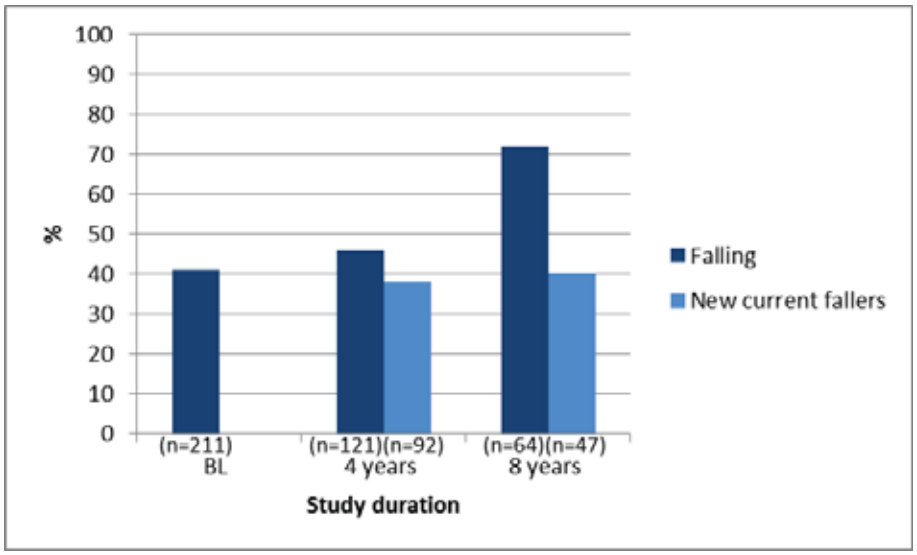

Figure 5. Evolution of falls in a population-based cohort with established PD during 8 years of follow-up.

6.3 Paper III

During 7 years of follow-up, 64.1% of the patients reported falling, with a RR of 3.1 or higher compared with NCs (Figure 6). The 7-year cumulative incidence of falls was 57.5% among 153 non-falling patients at baseline. Higher age, PIGD phenotype, higher UPDRS motor score and follow-up time were concomitants of falls during the study period. Independent risk factors of incident falls during follow-up were higher age at baseline, PIGD phenotype at 1-year visit and follow-up time.

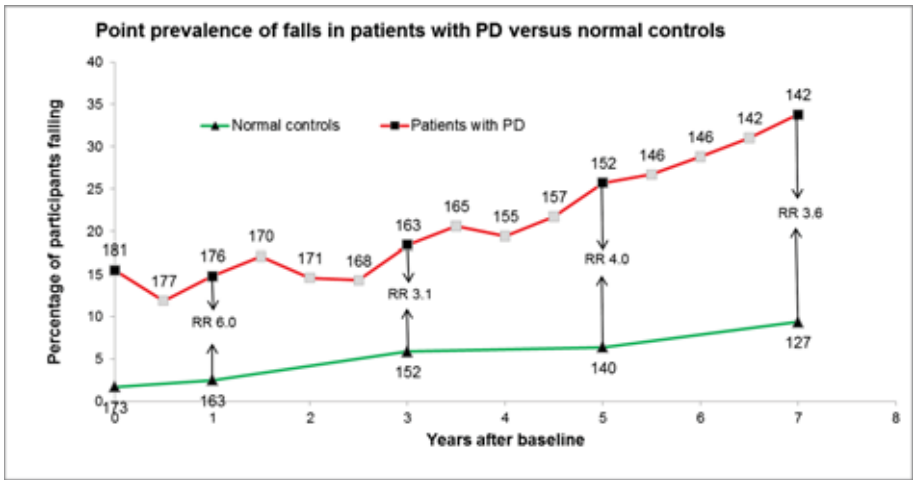

Figure 6. Evolution of point prevalence rates (%) of recent falls in newly diagnosed patients with PD and matched normal controls over 7 years. Main visits are colored black and figures indicate number of participants.

6.4 Paper IV

Patients with a fall history spent more time sedentary and less time standing compared with non-falling patients. We found no differences regarding volume of ambulatory activity, pattern or variability of sedentary behavior, standing or ambulatory activity in falling vs non-falling patients. Confidence in being able to get up from floor contributed significantly to time spent in sedentary behavior and ambulatory activity among those with a fall history, whereas motor impairment was significantly associated with time spent in all facets of physical activity among non-falling patients.

7 Discussion

7.1 Methodological considerations

The main strength of this PhD project is the large representative cohorts of patients with PD derived from 2 geographically-defined populations and the longitudinal design. Because several strategic steps were made to ascertain representative cohorts during recruitment, the risk of selection bias (i.e. a systematic error related to failure in the procedures used to establish a representative cohort)[146] is considered low. In longitudinal studies, high drop-out rates may lead to less representative remaining cohorts. For example, in paper II we followed a cross-sectional cohort with established PD for 8 years. At 8 years of follow-up, the remaining patients (64 patients out of 232 at baseline) may certainly have been a "selected" subsample of younger patients with less disease severity compared with the original sample. Although this is part of the natural development in longitudinal studies, we were unable to perform meaningful multivariable analyses to identify baseline risk factors for current falling at 8-year follow up. Nevertheless, a major strength of this study is the low attrition rate due to causes other than death, indicating a lower risk of selection bias.

One methodological challenge in this project is the falls outcome variable. We used items 13 and 14 from the UPDRS ADL part, reflecting the participants own opinion of their current fall status. Ideally, we would have preferred information from several specific questions about falling, preferably prospectively collected and related to a predefined time period. Prospective monthly fall diaries are the gold standard of falls assessment.[60] However, this approach is not practical in large longitudinal population studies as they may be too time consuming and lead to inconsistent reporting and drop-out after a short while. Sensors and falls detectors that collect, store and process a huge amount of objective data related to falls with minimal inconvenience for the participants, are potential and promising methodological improvements for future falls studies.

Noteworthy, a high occurrence of falls takes place in children learning to walk,[147] and may also be more common in athletes performing challenging motor tasks. Although injurious falls may occur in all ages, the combination

of a high prevalence and high susceptibility to injury in patients with PD is a major concern. Therefore, combining our data with medical records of fall-related injuries and data from the Norwegian hip fracture register is a possible methodological extension of this thesis.

Even an event such as a fall on an icy road is part of a complicated causal mechanism that involves many component causes. In this thesis, we have mainly focused on predictive variables within the individual, emphasizing PD-specific symptoms and signs. One potential disadvantage of this approach is the underestimation of other explanatory variables, such as weather condition and risk factors in the patients' home. Furthermore, the number of possible risk factors for falls is too high and complex to integrate in one simple model. Consequently, an evaluation of generic risk factors as well as disease-specific risk factors is recommended for high-risk patients with PD.[148] Furthermore, neither the Stavanger Parkinson nor the Norwegian ParkWest projects were solely designed to examine the natural development of falls in PD. Therefore, clinical examinations, detailed balance reactions, muscle strength and gait disturbances were not included in the examination protocols. We therefore aimed to examine predictive features and report explained variance (adjusted R^2) in linear regression models in paper IV.

Information bias can also arise when the information collected is erroneous, e.g. measuring variables that results in different quality or errors in the data file.[149] For example, an evaluation of the activPAL showed that placement of a sensor on the least affected leg generated less underestimation of steps in older people with impaired function.[140] In addition, step counts during slow walking speeds (0.47 m/s or slower) underestimated step counts in these people.[140] Because patients with PD may have slower gait, precautions regarding comparisons of step counts between studies are necessary.

Quality assurance of data took place in several stages of the research presented in this thesis. In both the Stavanger Parkinson and Norwegian ParkWest studies, standardized examinations and interviews were performed by neurologists and study group members experienced in movement disorders. During medical examination, patients were asked about the presence of different disease-specific symptoms that were translated into

categorical answers (yes or no) or ordinal figures (ranging from 0 [no symptoms] to 4 [marked presence of the symptom]) by the examiner. Although the medical examination and rating scales used have shown good validity and reliability,[150] misclassifications in these situations are possible. To further enhance study quality, ParkWest meetings were conducted twice annually to discuss protocols for gathering information and make sure recording forms had clear instructions. Furthermore, whenever data were entered into the database, values for a given case were double-checked for accuracy, missing values, outliers and consistency between visits.

Misclassification of subjects as non-fallers instead of fallers is another possible information bias. Considering the 4-year periodically recall of falls in the Stavanger Parkinson project, we suspect that underreporting of fall events may have occurred. This recall bias is probably also related to the consequences of falls, in particular memorizing non-injurious falls. To address this concern, patients in the Stavanger Parkinson project were urged to bring caregivers along to support, memorize and verify data during assessments. In addition, all patients with MMSE scores lower than 28 were accompanied by caregivers. In the Norwegian ParkWest study, the recall period for patients with PD was shortened to only 6 months intervals. Since control subjects were examined every 2 years (except between baseline and 1-year visit), the recall period was not identically between patients and controls by design. However, as UPDRS items 13 and 14 are not related to a specific time period, participants were in general asked about symptoms and signs since last visit to determine the frequency of falling. In paper IV, the methodology was additionally improved by asking questions about falling more than once during an interview, and adding questions emphasizing the circumstances surrounding falls to facilitate recall.

Several studies have shown that previous falls are associated with future falls. The predictive effect of previous falls, however, is most likely a blend of whatever effect previous falls has by itself and the effect of an unknown variable that is closely correlated with previous falls. This could indicate a much stronger relation between previous falls and future fall. In other words, previous falls might be a proxy for an unidentified event or feature more directly associated with the occurrence of falls. When these events are

identified, we may ultimately find that previous falls have less predictive effect after taking into account the biologic changes that are correlated with previous falls. This underscores the need for longitudinal studies of the development of falls in PD, excluding previous fallers in multivariable risk analyses. More importantly, from a clinician's point of view, prediction models should be able to identify patients at high risk before sustaining a serious fall.

Random errors can be explained as the variability of data that cannot be readily explained.[149] Within this thesis, paper IV with 48 participants may be the study at highest risk of random errors because of the relatively small sample size. To indicate the precision or lack of precision, the 95% CIs were reported.

Missing data occur frequently in longitudinal studies and may occur either by design (e.g. specific tests or examinations only scheduled to be performed at 5 out of 15 visits), at random (e.g. participants failed to complete a questionnaire or the examiner failed to fill in all figures), or not at random (e.g. participants with a recent fall history are more likely to miss a clinic appointment because of comorbidity issues).[151] Traditional complete case analyses were performed in paper I, II and IV, which may have reduced the sample size and led to wider CIs. Therefore, multiple imputations were performed in paper III to deal with this problem.

7.2 Falls in newly diagnosed vs established PD

Although 1 or more annual falls within 3 years of PD onset are considered a red flag signaling atypical parkinsonism rather than PD,[15] we found that patients with a mean motor onset of slightly more than 2 years before baseline had a RR of falling of 8.9 compared with normal controls (paper III). The RR decreased 6 months after baseline, and thereafter increased to baseline level within 3-4 years of follow-up, with a more than 3- fold RR of falls compared with NCs. More than ¼ of drug-naïve patients with incident PD reported falling at baseline or within the first year. Compared with these drug-naïve patients, the cross-sectional cohort with established PD had a 10-fold increased risk of falling (paper I). These findings suggest that the number of

patients sustaining a fall corresponds to the progression of the disease. We therefore examined the evolution of falls in both study populations further. Figure 7 shows the findings from our 2 population cohorts compared with previous published falls data from other incident cohorts. The most striking difference was observed between the ICICLE and the Norwegian ParkWest

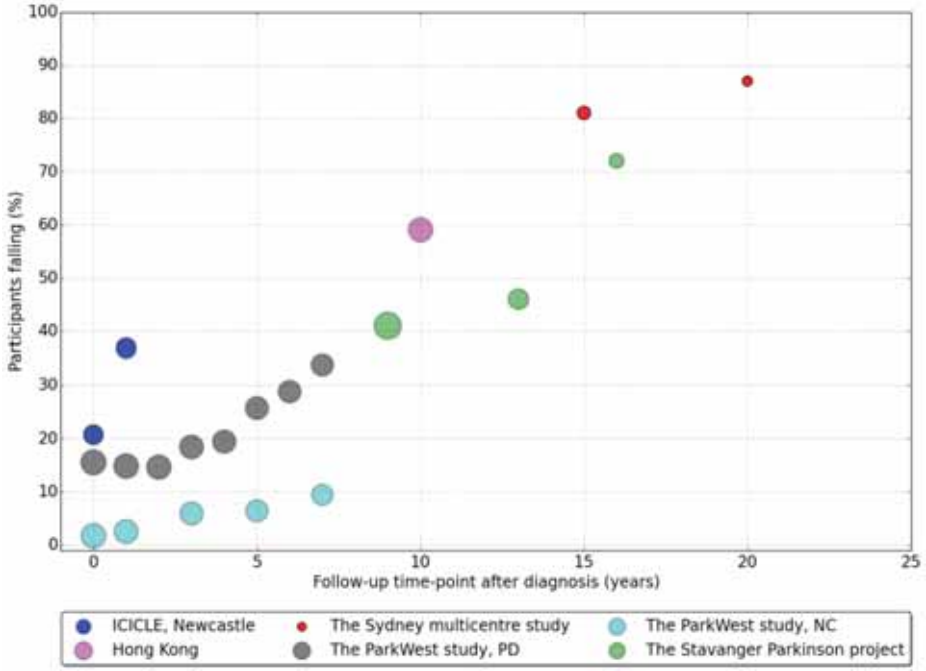

Figure 7. Development of falls in incident cohorts of patients with PD vs results from the Norwegian ParkWest study and the Stavanger Parkinson project. Dot sizes correspond to number of participants, range 30-211.

studies within the first year of follow-up, probably due to methodological issues. Whereas the ICICLE study used fall diaries with monthly reporting and regular telephone calls, the remaining studies asked participants about falls at periodically intervals ranging from every 6 months to 10 years. As discussed in section 7.1, the latter methodology probably caused an underestimation of the number of subjects falling.

Only a few studies have reported prospective falls in patients with PD without falls in the previous year. In a meta-analysis published almost a decade ago, incident falls were reported in 21% of patients with PD during a short period of 3 months,[71] whereas 2 other studies reported that 31% of patients with PD

had incident falls during 12 months of follow-up.[73, 90] Excluding previous falling patients in the Stavanger Parkinson project, 38% and 40% reported incident falls at 4 and 8 years of follow-up, respectively. These numbers are higher when compared with results from the Norwegian ParkWest study at 1 year (13%), suggesting that the methods of collecting falls data, especially the periodically interval, had an impact and/or that differences in study cohorts influenced these numbers. Whereas the Norwegian ParkWest study recruited drug-naïve patients with newly diagnosed PD from the general population, patients in the 2 aforementioned studies[71, 73] were cross-sectional and followed up for only 1 year or less. Although PD may be misdiagnosed at the time of diagnosis, the long follow-up time in the Norwegian ParkWest study using strict diagnostic criteria led to exclusion of 19 participants who did not have PD, and 2 of the NC subjects were excluded due to incident PD during follow-up. Therefore, the risk of having included subjects with atypical parkinsonism who tend to fall more frequently early in the disease course is considered low.

7.3 Concomitants of falls in PD

In paper I, we found a substantial higher frequency of falls in PD patients with H&Y stage ≥ 3 vs lower stages (Figure 3). Because H&Y is highly correlated with other measure of disease progression, such as UPDRS motor score and Schwab and England score,[152] we chose UPDRS ADL and UPDRS motor complications of therapy as independent variables in the final association model. In comparison, one prospective study[75] using data extracted from fall diaries identified walking, turning and standing as the 3 main activities at time of fall and found freezing as the most frequent symptom at time of fall. In line with these findings, we found that freezing of gait and axial impairment were significantly associated with falling in our cross-sectional cohort with established PD at 4-year follow-up (paper II), suggesting that ambulatory activity and standing are important aspects of ADL to examine further.

In paper III, age at baseline, UPDRS motor score, PIGD phenotype and follow-up time were independently associated with falls during 7-year follow-up of the incident PD cohort.

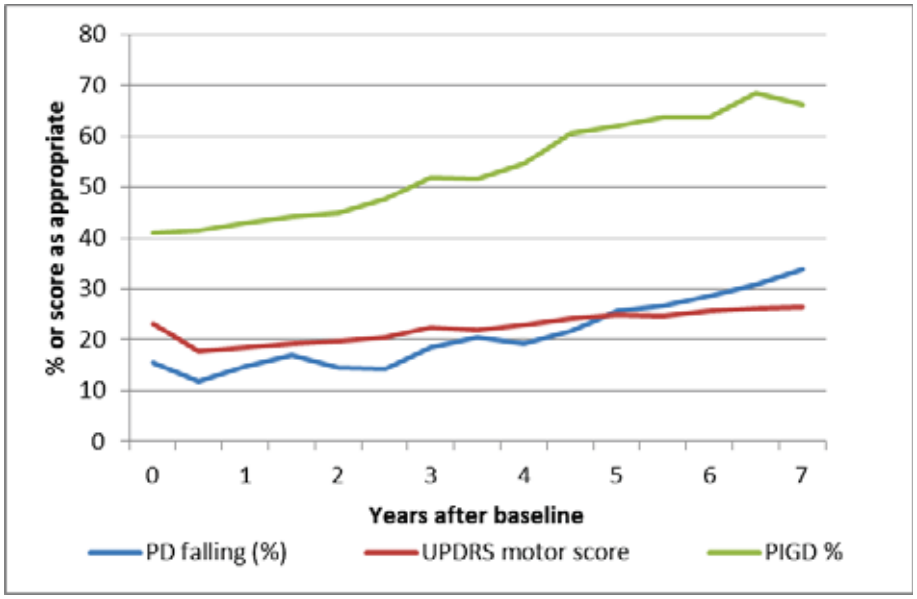

Figure 8. Evolution of point prevalence rates (%) in newly diagnosed and drug-naïve patients with PD over 7 years. PIGD phenotype (green line), recent falls (blue line) and the clinical disease progression of UPDRS motor score (red line).

Figure 8 illustrates the association between evolution of falls, severity of motor symptoms, and PIGD phenotype, and also captures the initiation of dopaminergic treatment at baseline in the newly diagnosed PD cohort. Of notice, motor symptoms improved during the first 6 months, and thereafter reached baseline levels within 3-4 years of follow-up. Whereas the association between falling and PIGD phenotype in the cross-sectional cohort with established PD (paper I) did not reach statistical significance (OR 3.3; p=0.093), this association was robust in the incident PD cohort (OR 4.3; p<0.001) (paper III).

Normal aging and comorbidity affecting components of musculoskeletal and sensory system can contribute to postural instability.[64] However, comparing normal age- and sex-matched controls with PD patients in the Norwegian ParkWest study underscored the impact of PD-specific symptoms on falling. Visual impairment is common in PD and contributes independently to gait disturbances such as reduction in gait speed and step lenght.[25] In addition,

exposure to levodopa has been associated with polyneuropathy in PD, causing a 5-fold higher prevalence of reduced peripheral sensation in patients compared with normal age- and sex-matched controls.[24] Because postural stability also requires complex central processing (e.g. integration of sensory information and control of body movement), deficits in attention and dual tasking have been suggested to increase the risk of falling.[118] For these reasons, assessments incorporating more detailed facets of postural instability and gait disturbances may yield better information in future studies as to the underlying deficits in PIGD associated with falls in PD. Nevertheless, the PIGD phenotype seems to be related to falls in both newly diagnosed and more advanced cases of PD. In line with this finding, a previous study found that the transition from tremor dominant to PIGD motor phenotype over time was unidirectional and irreversible,[153] a development in agreement with the progressive nature of PD.

The association between older age at baseline and falls appears less clear. Age at baseline was associated with falls in newly diagnosed PD patients (paper III), but showed only a trend toward significance (p=0.066) in the cross-sectional cohort (Paper I). This finding suggests that the association between age and falls becomes less apparent as the disease severity increases. Furthermore, age showed little predictive value in the meta-analysis by Pickering and colleagues,[71] and was not associated with recurrent falls in a recent review.[70] One possible explanation may be that age is associated with both disease development and falls, and therefore becomes less influential in studies of shorter durations.

7.4 Risk factors of falls in PD

Previous falls are considered a major risk factor for falls, both in the general population and in patients with PD. Given the potential severe consequences of falls,[98] it is of outmost importance to identify patients at risk of falling as early as possible, before sustaining injuries. In non-falling patients with newly diagnosed PD, we found that age at baseline, early PIGD phenotype and follow-up time were independent risk factors for falls. While age increased the risk of falling with 8% for every additional year in the newly diagnosed PD population, age was not a risk factor in the cross-sectional cohort with established PD. This finding suggests that age becomes less predictive of falls

in more advanced cases of PD, probably because of progression of symptoms and frailty as a result of the widespread pathology in the nervous system accompanied by deconditioning.

Freezing of gait predicted incident falls (OR 6.6; p=0.033) in our cross-sectional cohort with established PD in paper II, but not in the incident PD cohort in paper III. These findings may seem inconsistent at first, but considering the 4 year time interval between study visits in the cross-sectional cohort, the severity of freezing or closely related features to freezing of gait may have developed during this time. Furthermore, freezing of gait is more frequently reported in advanced cases of PD, and paper III might have been underpowered to show a significant effect in newly diagnosed patients. Future studies should include objective measures using novel technology as a more subtle measurement of gait disturbances.

Whereas the PIGD phenotype may be more useful in clinical settings, motor subscore B reflects the severity of non-levodopa-responsive motor symptoms in more detail. Therefore motor subscore B was chosen as a potential predictor of falls instead of the PIGD phenotype in paper II. Nevertheless, both the PIGD phenotype and motor subscore B includes non-levodopa-responsive motor symptoms that contribute to the prediction of future falls, suggesting that falling are related to the biology of non-dopaminergic pathways. In support of this, brain cholinergic deficits have been associated with falls,[154] slower gait speed[10] and postural instability[155] in patients with PD. Although more high quality studies are warranted to conclude, a recent randomized, double-blind, placebo-controlled study of 130 patients with PD (H&Y stage 2-3) demonstrated benefits in the group treated with acetylcholinesterase inhibitors in terms of improved measures of gait stability and a reduction of 45% in the rate of falls per month.[156] These encouraging findings suggest that acetylcholinesterase inhibitors may improve the management of patients with PD at high risk of incident falls.

7.5 Physical activity and falls in PD

In paper IV, we found that patients with PD who reported falls during the last 6 months were more sedentary and spent less time standing than non-fallers. While the interpretation of these findings is not straightforward, sedentary

behavior may be a consequence of a fall-related injury or fear-avoidance of physical activity. On the other hand, because ambulatory activity and standing are important to maintain muscle strength, bone density and balance, falls may also be a longitudinal consequence of sedentary behavior due to deconditioning or frailty. Nevertheless, a physical active lifestyle is recommended in patients with PD.[35] We therefore examined potential contributors to volume of sedentary behavior, standing and ambulatory activity further.

Whereas motor symptoms had an effect on the amount of physical activity among non-fallers, a perceived confidence in being able to get up from floor was strongly correlated with the amount of ambulatory activity and sedentary behavior among PD patients with recent fall. This may be related to experienced difficulties in getting up from floor after having sustained falling. Interestingly, none of the patients with recent falls had severe fall-related injuries affecting the mobility, and disease severity was comparable to the non-falling group. We therefore believe that these findings represent a different dimension to frailty not captured with the UPDRS motor scale and FES-I. Nevertheless, regular practicing strategies to get up from floor may have several benefits, including maintenance or even increased muscle strength in the lower extremities, as well as increased balance and possibly a more active lifestyle.

Increased volume of sedentary behavior has not been demonstrated in PD, but was reported in community-dwelling elderly men who had fallen 2 or more times last year.[116] Other researchers have examined selected aspects of ambulatory activity as predictors of future falls in PD. For example, Weiss and colleagues[86] explored objective measures using raw accelerometer data of gait and found that increased step-to-step variability (e.g. anterior-posterior width of the dominant frequency) predicted time to first fall. Although these qualitative measures of gait seem promising, data from this study are difficult to interpret in clinical practice. The same research group also developed an algorithm to detect missteps during free-living monitoring. Nine out of 40 patients reporting 2 falls or more in the 6 months prior to the study were significantly more likely to have a misstep during the 3-days recordings compared with non-fallers.[157]

A longitudinal study with repeated measures of physical activity and sedentary behavior may be useful to determine the order in what comes first. ActivPAL, when ordered in October 2012, was one of few available triaxial monitors on the commercial marked. Today, there are several monitoring technologies available. However, the activPAL was recently suggested as one of several monitors for use in PD.[158] Although an accelerometer provides objective measures of physical activity with minimal errors compared with self-report measures, the activPAL did not measure behaviors such as cycling or activities involving the upper body. Because patients were instructed to remove the device during bathing, activities such as swimming and hydrotherapy were not recorded. During interviews, however, patients were asked whether they had removed the accelerometer during programmed wearing time, and only 1 patient reported removing the device during an 1-hour swim.

Since motor symptoms often fluctuate and may be triggered by task, social settings and environmental challenges that cannot be replicated during a short clinical examination, wearable technology can provide unsupervised longitudinally data. The possibilities and potential of real world monitoring may therefore provide important insights into clinically relevant features, impact of therapy, and personalized treatment in future studies.[159]

7.6 Clinical implications and future research

Although the results of this thesis should be interpreted with the methodological considerations discussed earlier in mind, the findings have some potential implications for future research and management of PD patients.

To begin with, subtle objective measures of postural abnormalities including gait difficulties are recommended in future studies to address the slowly progressive, yet fluctuating nature of PD. There are only a few high quality intervention studies targeted to reduce falls in PD, therefore, clinical guidelines to prevent falls in PD lack sufficient evidence. Rather than assuming that patients with PD are a homogenous group, future studies should target specific disease stages or different subgroups of patients. A key finding

in this thesis is that early identification of patients at higher risk of falling is possible. As a consequence, newly diagnosed patients with PIGD symptoms and higher age may be considered prime targets of specialized assessment and treatment interventions. Finally, since falls in early PD are more common than previously recognized, more than 1 annual fall within the first 3 years of motor onset may not be a clear exclusion criterion for PD. Therefore, careful examination is important to ascertain definite PD.

Patients and care providers need to be aware of a general increase in sedentary behavior among patients with PD, and especially in patients who have suffered a recent fall. Patients may benefit training strategies to get up from floor to maintain or improve motor functions, and even improve selected aspects of physical activity. In accordance with the 2014 European Physiotherapy Guideline for PD, the insights from working with this thesis also support that referral to physiotherapists should be considered as soon as the PD diagnosis is suspected and especially after the "honeymoon period" to prevent inactivity and fear of moving or falling. In addition, a multidisciplinary care model of collaboration between professionals may facilitate early identification and targeted management of patients with higher fall risk.

8 Conclusions

The 4 included studies in this thesis have provided new knowledge about the evolution of falls during disease progression and identified disease-specific associated features and predictive symptoms for future falls. Finally, potential impact of recent falls in terms of maintaining an active lifestyle has been explored. The highlight findings include:

- Patients with PD fall more frequently than NCs during all stages of disease.
- Non-falling patients with incident PD have a more than 3-fold increased risk of falling during follow-up compared with NC subjects.
- Newly diagnosed patients with early PIGD and older age at disease onset have increased risk of falling.
- Symptoms representing non-dopaminergic deficiency (higher motor subscore B) and freezing of gait are associated with incident falls over 4 years in established PD without recent falls.
- Patients who have sustained a fall are more susceptible to being sedentary. Practicing how to get up from floor may be beneficial in patients at risk of falling
- The complex heterogeneity of PD and identification of patients who are moving in and out of a frailty continuum remains a challenge for future research.

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Paper I

Paper II

Paper III

Paper IV