Parkinson's Disease with Device, Diary, or in Disguise. Dyskinesia reduction, motor state evaluation, and workforce participation among persons with Parkinson's disease.

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2021

Document Version:
Publisher's PDF, also known as Version of record

Link to publication

Citation for published version (APA):

Total number of authors:
1

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Parkinson’s Disease with a Device, Diary, or in Disguise

Dyskinesia reduction, motor state evaluation, and workforce participation among persons with Parkinson’s disease.

Jonathan Timpka

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DOCTORAL DISSERTATION
by due permission of the Faculty of Medicine, Lund University, Sweden. To be defended at Segerfalksalen, Biomedicinskt centrum, Lund on November 19th, 2021 at 09:00.

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INTRODUCTION: In the wait for disease-modifying treatment for Parkinson’s disease (PD), efforts towards improved symptom control and reduced negative effects of PD can result in meaningful change for patients. The general efficacy of levodopa-carbidopa intestinal gel (LCIG) in advanced PD has been established, but its effects on dyskinesia need more investigation. The PD Home Diary has been used in clinical trials to evaluate treatment effects for almost 20 years, but needs to be validated. As treatments improve, it is vital to understand how PD affects workforce participation to further reduce the personal and societal effects of PD.

AIMS: The overarching aim of this thesis is to increase the knowledge on how health services can support persons with PD. The thesis has two main themes: motor fluctuations and workforce participation. Firstly, the aim was to contribute to a better understanding and utilization of existing tools in the treatment and evaluation of motor fluctuations in PD: LCIG and the PD Home Diary. Secondly, the aim was to improve our understanding of the impact of PD on workforce participation.

METHODS: Two clinical observational studies were used to investigate the effects of LCIG on dyskinesia and to validate the PD Home Diary, while one cross-sectional and one longitudinal registry study was designed to investigate workforce participation among persons with PD.

RESULTS: LCIG was found to reduce dyskinesia among persons with advanced PD and troublesome dyskinesia at baseline. Motor state assessments from the patient-reported PD Home Diary and those by an experienced observer were found to be in fair agreement. Workforce unavailability was found to be associated with anxiety among working-age persons with PD. Persons with a first sick-leave due to PD exhibited increased sickness absence in the preceding five-year period compared to controls, particularly due to musculoskeletal diagnoses.

CONCLUSIONS AND IMPLICATIONS: LCIG is a feasible treatment also for persons with advanced PD and troublesome dyskinesia. The PD Home Diary should not be regarded as interchangeable with the observer assessment gold standard. The association between workforce unavailability and anxiety needs further investigation, but anxiety should nonetheless be treated when identified. Musculoskeletal sickness absence is significantly increased in prodromal and early PD, which emphasizes that functioning and workforce participation is likely to be affected already at the time of diagnosis and thus demands immediate attention.

Key words
Dyskinesias, Employment, Levodopa, Parkinson Disease, Patient Reported Outcome Measures, Sick Leave

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Parkinson’s Disease with a Device, Diary, or in Disguise

Dyskinesia reduction, motor state evaluation, and workforce participation among persons with Parkinson’s disease.

Jonathan Timpka
“Om de fara till de varma länder, eller om de vila på sjöbotten med svalorna, är ännu ovisst”

Carl von Linné, on the stork,
Travels to Scania (1751).
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Abstract

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List of Papers

INCLUDED IN THE THESIS


ALSO BY TIMPKA ON PARKINSON’S DISEASE

*Original articles*


Review articles


Book


Book chapters


Thesis at a Glance: Q&A

PAPER I: LEVODOPA INFUSION & DYSKINESIA

Q: Is levodopa-carbidopa intestinal gel a suitable treatment for persons with advanced Parkinson’s disease and troublesome dyskinesia?

A: My study shows that a switch to levodopa-carbidopa intestinal gel results in significant reductions of both dyskinesia duration and severity in persons with advanced Parkinson’s disease and troublesome dyskinesia. However, not every participant improved. Other studies have recently suggested that a preexisting mix of biphasic and peak-dose dyskinesia could be predictive of a worse outcome concerning dyskinesia after the initiation of levodopa-carbidopa intestinal gel.

PAPER II: DIARY VALIDATION

Q: Is the PD Home Diary a useful instrument for assessment of the motor state among persons with Parkinson’s disease?

A: The PD Home Diary has traditionally been favored as a primary outcome in clinical studies as it is patient-reported and void of clinician’s bias. In my study, I show that the assessments from the PD Home Diary often differ from the assessments considered the gold standard, which are those by a clinician with experience of PD. Thus, the PD Home Diary data could be of potential interest, but it should be interpreted with care and definitely not as interchangeable with the gold standard assessment.
PAPER III: WORKFORCE UNAVAILABILITY

**Q:** Which Parkinson’s disease symptoms are associated with workforce unavailability in persons in working age with Parkinson’s disease?

**&**

**A:** In my study, I found anxiety to be associated with workforce unavailability. However, the design of the study did not allow for conclusions on whether anxiety is a cause or the result of workforce unavailability. Longitudinal studies are needed to investigate the association further.

PAPER IV: SICKNESS ABSENCE

**Q:** Is sickness absence increased in prodromal and early Parkinson’s disease?

**&**

**A:** In my study, I found persons who were granted a first sick-leave due to Parkinson’s disease to have exhibited more sickness absence in the preceding five years when compared to controls. This was also true when looking more specifically at prior musculoskeletal sickness absence, while there was no difference between Parkinson’s disease cases and controls regarding historical sickness absence due to mental and behavioral disorders.
Abbreviations

AIMS  Abnormal Involuntary Movement Scale
CI  Confidence interval
COMT  Catechol-\(O\)-methyltransferase
DBS  Deep brain stimulation
H&Y  Hoehn & Yahr staging scale
ICD-10  10th revision of the International Classification of Diseases and Related Health Problems
LCIG  Levodopa-carbidopa intestinal gel
LEAP  Levodopa in Early Parkinson’s Disease
LECID  Levodopa-entacapone-carbidopa intestinal gel
MAOB  Monoamine oxidase B
MDS-UPDRS  Movement Disorder Society sponsored revision of the Unified Parkinson Disease Rating Scale
MoCA  Montreal Cognitive Assessment
OR  Odds ratio
ParkReg  Swedish National Quality Registry for Parkinson’s Disease
PD  Parkinson’s disease
PDQ-39  39-item Parkinson Disease Questionnaire
Q1-Q3  1\textsuperscript{st} – 3\textsuperscript{rd} quartiles
RDRS  Rush Dyskinesia Rating Scale
UPDRS  Unified Parkinson Disease Rating Scale
VALIDATE-PD  The Diagnostic Validity of the Hauser Patient Diary and Sensor Based Movement Tracking for Evaluation of Motor Fluctuations in Advanced Parkinson’s Disease Study Program.
Introduction

PARKINSON’S DISEASE IN ONE PAGE

Parkinson’s disease (PD) was first described by James Parkinson in 1817 in “An Essay on the Shaking Palsy” and received its current name by Jean-Martin Charcot during the 1870’s. PD is a progressive neurodegenerative disease characterized by four cardinal motor symptoms: shaking (tremor), slowness of movement (bradykinesia), stiffness (rigidity), and poor balance (postural instability). A PD diagnosis is based on the clinical examination, but repeated assessments are often needed to survey the disease progression and thus increase the accuracy of the diagnosis. Imaging methods or laboratory tests are not necessary for a PD diagnosis, but may help rule out other diseases with overlapping initial presentation.

In the late 1950’s and early 1960’s, a series of breakthroughs led to the understanding that there is a dopamine deficiency in the basal ganglia of the brain in PD and that symptoms are alleviated by administration of the dopamine precursor levodopa. Since then, a range of additional drugs have been developed, but levodopa remains the drug that all PD patients receive at some point during the disease course. The available drugs provide symptom relief and improve the quality of life for persons with PD, but do not cure or modify the disease progression.

Non-motor symptoms are known to influence the quality of life negatively and adequate control of non-motor symptoms is central to successful PD care. Constipation, anosmia, and mood or sleep disorders are early non-motor symptoms that sometimes arise long before the cardinal motor symptoms and might be early signs of PD (“in disguise”). Orthostatic hypotension, dementia, and hallucinations are typical non-motor symptoms that occur later during the disease course.

As the disease progresses, persons with PD often experience fluctuations in the symptom relief over the course of a day. The resulting motor states, particularly “on” and “off”, are thus central PD terminology. “On” represents a state in which the patient experiences more symptom relief and less disability. During “off”, motor symptoms such as rigidity, tremor, and bradykinesia become more noticeable.

The life expectancy with PD is near normal or normal in advanced healthcare systems, but there are negative effects on functioning, activities of daily living, workforce participation, and quality of life. This is particularly true in the advanced stage of PD, which typically occurs after 7-10 years.
RATIONALITY OF THE THESIS

Over the next sections, I will introduce the main concepts of the research area and put my papers in a context. However, I will first present the gaps-of-knowledge I set out to fill with this thesis.

If persons with PD were to wish for one scientific breakthrough, it would probably be for the discovery of a curative or disease-modifying PD treatment. In lieu of trying to find that treatment, I spent the planning of this thesis focused on identifying areas in which new knowledge could improve the support from the health services to persons with PD. This thesis is therefore based on four papers in which I investigate a set of unanswered questions throughout the PD process. A dividing line may be drawn between the two main themes of this thesis: motor complications (papers I and II) and workforce participation (papers III and IV).

Firstly, open-label studies of the device-aided levodopa-carbidopa intestinal gel (LCIG) treatment have repeatedly shown that LCIG reduces the time in “off” and increases the time in “on without troublesome dyskinesia”. However, before paper I, little was known of the effects of LCIG when significant parts of the day were not only spent in “off”, but also in “on with troublesome dyskinesia”. In paper I, I therefore report findings from a pilot study including participants that were particularly troubled by dyskinesia before the start of LCIG treatment.

In paper I, just as in many other clinical trials on PD since the early 2000’s, the PD Home Diary was used for measurement of motor states in a PD patient sample. The PD Home Diary is a patient-reported instrument which has several upsides that will be discussed later. However, despite being a central instrument in clinical PD research, the PD Home Diary was never validated against the gold standard for clinical assessment of PD motor states: the examination by an experienced clinician. I set out to do this comparison and the results are reported in paper II.

The gradual raising of the retirement age will result in an increase of the PD prevalence in the working age population. An increasing number of persons with PD will thus be participating in the outskirts of the workforce and will be in need of support to sustain their working ability. Certain PD symptoms are likely to be more strongly associated with a decrease in workforce participation. If these symptoms are identified, that knowledge could be used to tailor the support for persons with early-to-mid-stage PD in their continued working life. In paper III, I investigated the association between a number of PD symptoms and workforce participation.

Lastly, the prodromal stage of PD is long and early symptoms of PD may appear years before the emergence of cardinal motor symptoms. For paper IV, I was interested in whether this is evident through an increase in sickness absence leading up to and around the time of a PD diagnosis. This could potentially help point out symptom clusters suitable for early intervention following a PD diagnosis.
MANAGEMENT OF MOTOR COMPLICATIONS

At the time of diagnosis, the PD symptoms are often only noticeable on one side of the body. Patients themselves tend to notice the emergence of a resting tremor, while friends and family may have noticed an increasingly stooped posture or a reduction in automatic movements, such as reduced arm swing during walk. Treatment is typically initiated immediately after diagnosis to reduce the short-term disability and improve quality of life. Oral levodopa serves as the gold standard for treatment of PD and is an effective treatment in the early stages of PD—sometimes to the extent that PD motor symptoms more or less disappear for some time.

As PD progresses, symptoms become bilateral despite increased daily doses of levodopa and the addition of other antiparkinsonian drugs. Within a few years, some patients start to notice dyskinesia and motor fluctuations. Dyskinesia is involuntary movements that can be divided into chorea (twitching or jerking movements) and dystonia (involuntary postures or limb positioning). Motor fluctuations are recurring periods with an insufficient effect of treatment on motor symptoms, often before the intake of the next dose (“wearing off”). After 4-6 years of treatment with oral levodopa, at least 40% of patients develop significant dyskinesia and motor fluctuations, and almost all patients are affected after 10 years. After the initial adjustments, the motor complications become increasingly difficult to manage using conventional oral and transdermal medication. The motor complications are at least in part the result of fluctuating plasma concentrations caused by the oral, pulsatile distribution of dopaminergic medication. Oral medication is also dependent on the passage through the stomach and, as delayed gastric emptying is very common in persons with PD, this may result in an erratic medication response.

Levodopa is a prodrug of dopamine and is, unlike dopamine, able to cross the blood-brain barrier. Levodopa is always administered together with a dopa decarboxylase inhibitor such as benserazide or carbidopa, which reduces conversion of levodopa before entry into the central nervous system. The dopa decarboxylase inhibitors are unable to cross the blood-brain barrier and do not prevent the conversion from levodopa to dopamine within the brain. As the half-life of levodopa is as short as 1.5 h, it is important that the passage through the stomach to the site of absorption in the small intestine is not delayed from gastrointestinal motility disorders. Otherwise, patients may start to experience “wearing off”, delayed “on”, and an unpredictable response to their routine medication. As the disease progresses, the ability of dopaminergic neurons to buffer dopamine decreases, the plasticity in the striatum is reduced, and the variations in dopamine concentration become increasingly non-physiological.

Besides levodopa, patients are often prescribed dopamine agonists, catechol-O-methyltransferase (COMT) inhibitors, or monoamine oxidase B (MAOB) inhibitors to reduce the PD symptoms during the course of the disease. Dopamine agonists
mimic the effects of dopamine by binding to and activating dopamine receptors, while COMT and MAOB inhibitors increases brain dopamine levels by increasing the bioavailability of levodopa and reducing the metabolization of dopamine, respectively. Amantadine is often used as an add-on to reduce dyskinesia and is thought to do so via blocking of N-methyl-D-aspartate receptors.  

Historically, there has been a debate whether levodopa should be avoided in the early disease stages when drugs such as dopamine agonists, MAOB inhibitors, and amantadine, together or on their own result in acceptable symptom control. The hypothesis was that this would delay the development of motor complications. However, that hypothesis has been disputed by the Levodopa in Early Parkinson (LEAP) trial wherein patients receiving early-start levodopa treatment did not differ from those receiving delayed-start levodopa treatment in the prevalence and severity of motor complications in the long-term. As levodopa gives the best early symptom relief, the recommendations are now to start with levodopa as the first-line drug for newly diagnosed PD patients, but to use the lowest effective dose.

There is no uniform definition of when a person has reached the advanced stage of PD, but there is consensus that the degree of symptom control during “on” and “off”, as well as worsening tremors, bradykinesia, gait problems, and cognitive problems

![Diagram](image1.png)

**Figure 1.** Levodopa plasma concentration and simplified sketch of the narrowing of the therapeutic window over the course of Parkinson’s disease. Adapted from Timpka J et al. Nonoral continuous drug delivery techniques in Parkinson’s disease: for whom, when, and how? Mov Disord Clin Pract 2016 Mar 24;3(3):221-229.
could be indicative of advanced PD. Persons with advanced PD are still responsive to levodopa, despite a reduction in the clinical effect of the treatment. This is in part explained by the narrowing of the therapeutic window over time (Figure 1), meaning that patients become increasingly prone to side effects due to either high or low plasma concentrations of levodopa. This makes treatment with oral immediate-release levodopa, which has a short half-life, difficult. The 5-2-1 rule (Figure 2) has been suggested as a screening tool for when patients with advanced PD need optimization of treatment. This builds on the initial response to emerging motor fluctuations, which is to make sure that the daily levodopa intake is spaced out over at least five doses to reduce the peak plasma concentration of levodopa. If the patient despite this spends more than two hours in “off” or more than one hour in “on with troublesome dyskinesia” per day, the pros and cons of device-aided treatment for the respective patient should be considered.

There are currently three main concepts of device-aided treatment that are available for treatment of patients with advanced PD: subcutaneous apomorphine infusion, deep brain stimulation (DBS), and intestinal levodopa infusion. There are pros and cons for each of the device-aided treatments, but the selection of treatment for a specific patient is also heavily influenced by local experience, traditions, and competence. There have been no randomized, placebo-controlled, head-to-head comparisons between all the device-aided treatments, but there is one real-life observational report. The report concludes that there are different profiles between the device-aided treatments for the effects on both motor and non-motor symptoms. At least two major open-label studies have dedicated to demonstrating the anti-

\[
\begin{align*}
5 & \geq 5 \text{ doses of oral levodopa per day} \\
2 & \geq 2 \text{ hours per day spent in "off"} \\
1 & \geq 1 \text{ hour per day spent in "on" with troublesome dyskinesia}
\end{align*}
\]

*Figure 2.* The 5-2-1 rule for identification of patients with advanced Parkinson's disease in need of treatment optimization.
The dyskinetic effect of subcutaneous apomorphine infusion, but the randomized, placebo-controlled trial by Katzenschlager et al. in 2018 did not show any significant dyskinesia reduction—possibly due to low baseline dyskinesia durations. The anti-dyskinetic effect of DBS of the subthalamic nucleus is well known. In the case of DBS, the reduction in the daily oral levodopa dose needed seems to be a significant contributing factor.

Intestinal levodopa infusion was introduced in the late 1980’s and early 1990’s. The most common form of intestinal levodopa infusion, LCIG, is an aqueous carboxymethylcellulose gel containing levodopa (20 mg/ml) and carbidopa (5 mg/ml). It is often given as a monotherapy, either during the waking hours or on a 24-h regimen. Using a portable infusion pump, the LCIG is continuously administered into the proximal part of the jejunum via a percutaneous endoscopic gastrostomy with a jejunal tube. The total daily dose of LCIG has three different parts: a morning bolus dose, the continuous maintenance dose, and, if required, extra bolus doses. Recently, a fourth device-aided therapy has been presented: levodopa-entacapone-carbidopa intestinal gel (LECIG). LECIG relies on the same principles as LCIG but uses another delivery system and, as the name suggests, also contains entacapone, which enables a reduction of the daily levodopa dose.

Many of the effects of LCIG treatment have been established, such as reductions in time in “off”, increases in time in “on”, and improvements of health-related quality of life. Early on, the most solid evidence of the efficacy of LCIG was presented in two randomized cross-over trials. The first large randomized, placebo-controlled trial on LCIG was published by Olanow et al. in 2014 and had a follow-up of 12 weeks. Patients with advanced PD were found to decrease their mean time in “off” and increase the mean time in “on” when switched to LCIG treatment. However, only non-significant reductions in time in “on with troublesome dyskinesia” were found. Other studies have shown improvements of dyskinesia, but make no distinction between troublesome and non-troublesome dyskinesia. Similar to the 2014 trial, studies on LCIG often present relatively short baseline durations in “on with troublesome dyskinesia” and results are thus difficult to interpret in terms of effects on dyskinesia. Thus, at the time of my paper I, there had been a number of indications on a positive effect of LCIG treatment on dyskinesia but the evidence was lacking.
MEASUREMENT OF MOTOR COMPLICATIONS

In the early 00’s Hauser et al. developed the PD Home Diary (“the Diary”) for use as an outcome measure of motor function in clinical trials.\textsuperscript{28-30} Before the introduction of the Diary, trials relied heavily on the reduction of time spent in “off” as an indicator of improved motor function. This focus on reduction of time spent in “off” does not take into account that an increase in dopaminergic stimulation might reduce the time in “off”, but may also increase the incidence and severity of dyskinesia. In addition to “on” and “off”, Hauser et al. added “on with non-troublesome dyskinesia” and “on with troublesome dyskinesia” to enable a more accurate depiction of the various motor states of PD.

Since its development, the Diary has been a central endpoint of many clinical trials on PD.\textsuperscript{31} This is primarily due to its ease of use and relative low cost during long-term follow-up, but also due to the limited clinician bias. Patient-reported outcomes such as the Diary are also given increasing attention as they highlight the patients’ experience of an intervention and may as such complement other outcomes for a more comprehensive assessment.\textsuperscript{32}

There was an initial effort for validation of the Diary; first through correlation between patient self-assessment of “on” or “on without troublesome dyskinesia” with “good” time, then “off” or “on with troublesome dyskinesia” with “bad” time.\textsuperscript{28} Hauser and colleagues then presented the test-retest reliability and predictive validity of the Diary.\textsuperscript{29} In the study by Hauser et al., the Diary was completed for three consecutive days in each of two consecutive weeks. The calculated Cronbach’s $\alpha$ coefficient indicated an acceptable internal consistency.\textsuperscript{33} However, the number of Diary errors increased after the third day of registration,\textsuperscript{29} which could indicate that participants start to lose interest in the Diary recordings and that more is not necessarily better in this regard.

In the setting of validation of the Diary, the predictive validity is used to describe how well the Diary ratings can be used to assess how persons with PD perceive the extent and severity of dyskinesia. To investigate this Hauser et al. calculated the Pearson correlations between visual analogue scale replies to five different questions and the corresponding information from the Diary (for example “How much difficulty did dyskinesia cause you today?” and “on with troublesome dyskinesia”). The Pearson correlation coefficient $R$ varied from .36 to .57 between the five items.\textsuperscript{29}

Persons with PD are known to have limited knowledge of motor state functional terms and need some training prior to the use of the Diary.\textsuperscript{30} Hauser et al. found that the study participants thought that an instruction video and a version of the diary with pictograms was helpful and made it easier to understand the different motor states.
Several technical solutions for measurement of motor function and motor complications in PD have been presented over the last few years, and more are in development. The solutions range from sets of sensors that are meant to be worn on all four extremities and on the trunk to those that are worn on one wrist like a watch. The more established products have not only entered clinical trials as an exploratory outcome measure, but also clinical practice to some extent. The potential benefit from the use of wearables is undeniable in both clinical and study settings as assessment of motor function during an extended period of time (days to weeks) is likely to be a more accurate depiction of the motor function than the snapshot seen during a visit with the neurologist. The unsupervised assessments have also been shown to differ from those supervised by the clinician. The ecological validity of these supervised tests is often found to be relatively low, meaning that a gait test done at the doctor’s office is not very representative of the patient’s gait in a real-life context. This is indicating that it is not only the short time spent at the doctor’s office that is limiting, but also that the assessment does not seem to be representative of the patient’s general situation. The possibilities for measurement of motor complications are expanding rapidly, but the methods need to be properly validated before the inclusion in clinical practice or as an outcome in clinical trials. There is certainly a need for caution in the interpretation of the results from new wearables as it is often not clear what they measure and how these assessments relate to established methods of measurement. This is to some extent true also for the Diary. Despite having been widely used to measure the PD motor state in clinical studies for almost 20 years, the resulting measurements have not been compared to what is considered the gold standard for clinical measurement of motor function in PD, which is the assessment by an independent observer with experience of PD.
**PD IN THE WORKFORCE**

PD is after Alzheimer’s disease the second most common neurodegenerative disease and it is becoming increasingly common in the workforce. The prevalence of PD varies greatly between studies, but meta-analyses have estimated the prevalence in Europe to 108-257/100,000 and, more recently, in Italy to 194/100,000.\textsuperscript{37, 38} However, both the incidence and prevalence of PD are typically increasing with age.\textsuperscript{37-40} Age is in fact the most significant risk factor for PD, but PD is far from a disease that is exclusively affecting older people. One in twenty persons with PD have been diagnosed before an age of 50 years, while 30% have been diagnosed before an age of 60 years.\textsuperscript{41}

A majority of the more economically developed countries are currently facing challenges with ageing populations that within 20 years will lead to a 50% increase in the number of persons living with PD,\textsuperscript{42} and an even greater increase is predicted for developing countries.\textsuperscript{43} It is therefore likely that it will become increasingly common to be diagnosed with PD during working age and the socioeconomic impact of PD will thus increase. The magnitude of the income loss due to a PD diagnosis varies partly depending on the social security and sickness insurance system, but a PD diagnosis around an age of 60 is likely to lead to a major income loss before the age of 80.\textsuperscript{44}

A person’s work ability is dependent on a range of factors beyond physical functioning, such as the type of work they are supposed to perform, their pre-existing skills, their motivation and drive, and the macrosocial environment. One theoretical model of work ability is the Work Ability House Model (Figure 3), which emphasizes the interdependence between the different dimensions of work ability.\textsuperscript{45, 46} The roof of the house—symbolizing work ability—rests upon four different floors: health and functional capacities, professional competence; values, attitudes, and motivation; and work conditions, demands, and management. The work ability depends on the balance between the different floors but is also affected by outside factors such as the support network in the form of the family and immediate social environment. However, the Work Ability House Model has not been tested in a population of persons with PD, rather Finnish teachers and Brazilian hospital workers,\textsuperscript{47} but illustrates how there is a range of factors other than those strictly caused by or related to a disease, in this PD, that could influence the work ability.
On the group level, persons who later will get diagnosed with PD have been reported to exhibit higher medical expenses and a lower employment rate up to eight years prior to the diagnosis in comparison with controls. However, the patterns through which early non-specific motor and non-motor symptoms affect workforce participation during prodromal and early PD have not been systematically investigated. Persons with PD that are still active contributors in the workforce often find it difficult upholding their current workload. In addition to loss of employment, other detrimental psychosocial factors such as stigma, marital discord, and depression are known to be more common in persons with young-onset PD. Altogether, this highlights both the challenges for individuals with PD to sustain a satisfactory working life and that work ability is a more complex construct than simply the physical ability to move oneself to the workplace and perform a set of routine work tasks.

When an employee gets sick in Sweden, the health services are responsible for the treatment and the sickness certification. The responsibility to coordinate rehabilitation efforts falls on the Social Insurance Agency and it may therefore involve not only the employee, employer, and health services, but also the Public Employment Service and the Social Services if needed.
significant responsibilities: if the sickness absence is estimated to be at least 60 days, the employer needs to establish a plan for the employee’s return-to-work.\textsuperscript{54}

Untreated persons with PD exhibit limitations in activities of daily living and self-reported health status at an early stage of the disease.\textsuperscript{55} In a questionnaire study among people with PD of working age, 82\% of those who worked full-time and 92\% of those who worked part-time reported that PD had worsened their working capacity.\textsuperscript{56} The same study showed that full-time employment without adjustment of work tasks is rare beyond the first two or three years of PD, while others have shown that PD typically leads to loss of employment within 10 years.\textsuperscript{49-51} In addition to being employed to a lesser extent than others of the same age, persons with PD miss an average of eight more work days per year due to health reasons.\textsuperscript{57}

The prodromal process starts early and may result in clinically meaningful symptoms; for example, there is a slightly increased risk for being diagnosed with PD during the 10 years following an injurious fall and 26 years following a hip fracture.\textsuperscript{58} There are indications that prodromal PD has significant negative effects on workforce participation, and that these early symptoms can be tied to current models of PD progression. Non-motor symptoms such as depression and anxiety are seen as part of the prodromal phase of PD and often arise at least 10-20 years prior to the onset of motor symptoms.\textsuperscript{59} PD pathophysiology is typically recognized to comprise progressive involvement of several brain regions, from the brain stem and the basic forebrain to the extrapyramidal system.\textsuperscript{60-62} The importance of a more thorough understanding of the prodromal phase by recording symptoms and clinical findings reflecting this pre-diagnostic process of PD has been highlighted.\textsuperscript{63}

Despite these known challenges already at the very early stages of PD, few studies have focused on exploring how PD affects the working ability of people of working age and what could be done to facilitate employment.\textsuperscript{64} This is despite the fact that the return to work have been shown to be an important factor in life satisfaction in other neurological disease, such as stroke,\textsuperscript{65} and that persons with PD often express that it in retrospect was a great personal loss to involuntarily stop working.\textsuperscript{56}

A first step towards facilitating workforce participation for persons with PD is the identification of factors contributing to an early loss of employment. A two-year randomized controlled study among employed people with PD found that levodopa and COMT inhibitor treatment was associated with lower absenteeism and—although not statistically significant—higher employment rates at the two-year follow-up than those randomized to levodopa and placebo treatment.\textsuperscript{67} This was hypothesized to be due to better effects on motor fluctuations and dyskinesia in the levodopa and COMT inhibitor group. Other studies have identified disease severity,\textsuperscript{56} depression, anxiety,\textsuperscript{68} and PD duration as predictors or contributing factors for workforce exit.\textsuperscript{50,56} In a post-hoc analysis of two studies from the United Kingdom, there were no significant differences in time to loss of employment
between sexes, types of work, rural vs. urban environment, living with a partner or not, or having children living at home or not.\textsuperscript{49}

The notion that the type of work does not seem to affect the time to workforce exit following the PD diagnosis has some additional support,\textsuperscript{51} but at least two studies show that white-collar workers and individuals with university education are able to continue their employment to a larger degree.\textsuperscript{50, 56} One explanation for these contradicting findings could be that the used dichotomizations between white-collar vs. blue-collar or high- vs. low-skilled labor are simply insufficient. For other disorders it is possible to distinguish an expected connection between work capacity and type of occupation.\textsuperscript{65, 69} For example, it is less likely that people with psychiatric illness return to emotionally demanding jobs, while those with musculoskeletal morbidity to a lesser extent return to professions with a demanding physical work environment (e.g., exposure to heat, cold, vibration, or strenuous working postures).

It is still not clear whether device-aided treatment could be useful as a tool to preserve the work ability among persons with PD. There is one study showing that working persons that receive DBS are likely to continue to work two years after the operation, but very few of those that had already left work prior to the operation returned to work—despite similar improvements of motor and non-motor symptoms between the two groups.\textsuperscript{70} Another study shows that a majority of patients working before the start of device-aided treatment still work after one year, but that most had retired or received disability pension after a median follow-up of five years.\textsuperscript{71}

PD is a complex disease with great inter- and intra-individual variations that give rise to both motor and non-motor symptoms at varying degrees. To facilitate continued workforce participation among persons with PD, symptoms and circumstances particularly detrimental for the work ability need to be identified. Together with a better understanding of when these problems arise, this knowledge could prepare the field for the designing of interventions aiming to reduce the negative effects of PD on workforce participation.
Aims

The overarching aim of this thesis is to increase the knowledge on how health services can support persons with PD. The thesis has two principal themes: motor complications and workforce participation. Specifically, I aim to contribute to a better understanding and utilization of already existing tools in the treatment and evaluation of motor fluctuations in PD (papers I and II), as well as to improve our understanding of the impact of PD on workforce participation (papers III and IV).

In paper I, the primary aim was to investigate whether the device-aided treatment LCIG improves dyskinesia in patients with advanced PD and troublesome dyskinesia. The secondary aim was to investigate the effects of LCIG on motor function and health-related quality of life.

Paper II focused on motor state assessments in PD with the aim to further validate the patient self-assessment PD Home Diary by investigating the agreement between observer and Diary ratings.

In paper III, the aim was to explore what specific PD symptoms that are associated with workforce unavailability among working age persons with PD.

In the final paper IV, the aim was to investigate whether persons diagnosed with PD exhibit increased sickness absence prior to a first sick-leave episode attributed to PD. An exploratory aim was to gain knowledge on whether the occurrence of and reason for sickness absence could identify individuals with prodromal PD (or PD “in disguise”) in order to allow early diagnosis and treatment.
Methods and Results

OVERVIEW OF METHODS AND DATA SOURCES

The study designs used for the papers in this thesis can be divided into two main categories: the clinical observation studies of papers I and II and the registry-based studies of papers III and IV (Table 1).

In paper I, I presented longitudinal data from a small sample of persons with PD starting LCIG treatment and the studied endpoints were therefore intra-individual pre-post comparisons. Both patient- and investigator-reported outcome measures were used to evaluate the effects of the treatment. In paper II, I focused on a specific patient-reported outcome measure, the PD Home Diary, and compared it to simultaneous gold standard observer assessments. Given the categorical data format, I used Cohen’s κ to determine the concurrent criterion validity of the PD Home Diary.

<table>
<thead>
<tr>
<th>Paper</th>
<th>Study Design</th>
<th>Recruitment/Data Source</th>
<th>PD stage</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>I: Levodopa infusion &amp; dyskinesia</td>
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<td>Outpatient clinic</td>
<td>Advanced</td>
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<tr>
<td>II: Diary validation</td>
<td>Clinical, longitudinal, open-label observation</td>
<td>Outpatient clinic</td>
<td>Mid-to-Advanced</td>
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<td>III: Workforce unavailability</td>
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<td>ParkReg</td>
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<td>IV: Sickness absence</td>
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<td>The Swedish Social Insurance Agency</td>
<td>Prodromal-to-Early</td>
<td>1074</td>
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</tbody>
</table>

PD, Parkinson’s disease; N, number of study participants; ParkReg, Swedish National Quality Registry for PD.
For the study presented in *paper III*, I used regional data from the Swedish National Quality Registry for PD (ParkReg). As ParkReg was new at the time of the study, the number of recorded visits was relatively low. I therefore used a cross-sectional design with binary logistic regression models and workforce unavailability as the outcome variable. At that time, there were approximately 1.3 million people living in Skåne. With a presumed prevalence of 200 PD cases per 100,000 inhabitants this would mean that the coverage of PD patients in ParkReg was around 15%.

For the study described in *paper IV*, I used the Support for Righteous Sick-leave database, which is compiled from the Swedish Social Insurance Agency’s registry Micro-Data for Analysis of the Social Insurance. The version used for the study covered 7.8 million sick-leave episodes. By identifying incident PD sick-leave episodes and matched controls, I used a retrospective case-control design with pairwise testing to investigate the historic sickness absence among persons with or without a sick-leave episode due to PD.

P < .05 was considered statistically significant in all papers of this thesis. The statistical analyses of *paper I* were primarily performed at the Institute of Biometry, Hannover Medical School, Hannover, Germany. I performed the statistical analyses of *papers II-IV* with the support of co-authors and named collaborators. For the thesis, I have reworked the descriptive statistics of *paper I* in order to better reflect the data and the non-parametric tests used. IBM SPSS Statistics versions 23.0-27.0 were used for analyses.

**ETHICAL CONSIDERATIONS**

The studies presented in this thesis were approved by the Ethics Committee of the Medical Association, Bremen, Germany (ref. 162); the Regional Ethics Review Board, Lund, Sweden (ref. 2013/374, 2015/391, and 2017/936); and the Regional Ethics Review Board, Linköping, Sweden (ref. 2014/462-31). Informed consent was obtained from study participants prior to enrollment in the studies herein presented as *paper I-III*. For *paper IV*, Swedish national government-owned register data was used. Thus, informed consent for the use of the data was not required from the included individuals.
Does initiation of LCIG improve dyskinesia in patients with advanced PD and troublesome dyskinesia?

This was a prospective, exploratory observational study with a follow-up of six months. The study took place at the Department of Neurology, Central Hospital, Bremerhaven, Germany. Persons with a diagnosis of idiopathic PD, ≥ 3 h per day in “on with troublesome dyskinesia” despite optimized treatment, and the ability to complete questionnaires and diaries were included. The exclusion criteria were: being pregnant, scoring lower than 24 points on the Mini Mental State Examination as an indicator of cognitive impairment, or exhibiting hallucinations or other psychotic symptoms.

The primary endpoint was time in “on with troublesome dyskinesia” according to a modified PD Home Diary. The secondary endpoints were time in “on without troublesome dyskinesia”, dyskinesia intensity scores on the Visual Analog Scale (VAS), Abnormal Involuntary Movement Scale (AIMS), Rush Dyskinesia Rating Scale (RDRS), and Unified Parkinson’s Disease Rating Scale (UPDRS) items 32 (dyskinesia duration) and 33 (dyskinesia disability). Additional endpoints were the UPDRS parts II and III, Parkinson’s Disease Questionnaire-39 (PDQ-39), UPDRS total, and time in “off”.

Figure 4. The relationship between the total daily dose and the three adjustable subsets of doses of levodopa-carbidopa intestinal gel infusion.
Patients received a percutaneous endoscopic gastrostomy with a jejunal tube, which was then connected to a portable infusion pump for the initiation of LCIG treatment. The LCIG treatment was first started with a maintenance dose (Figure 4) based on previous oral and transdermal dopaminergic medication by using an estimation of the daily dose equivalence to levodopa. During a hospital stay that ranged between 14 and 33 days, the maintenance dose was titrated in steps of 2 to 4 mg levodopa per h until an optimal clinical response was reached, which was a maximal time in “on” without any disabling dyskinesia. The participants were allowed to administer additional bolus doses of LCIG containing 20 to 50 mg levodopa in case they were experiencing episodes of bradykinesia. After discharge from the hospital, participants were able to contact study personnel for queries and were then followed-up after six months.

The participants were instructed to keep a modified PD Home Diary in which they once every waking hour noted whether they were in “off”, “on with troublesome dyskinesia”, or “on without troublesome dyskinesia”. The dyskinesia intensity was self-assessed on the VAS. Participants received instructions and training on the self-assessments by a study nurse until they reached 80% concordance with the nurse’s rating for “off” and “on” states. The modified PD Home Diary and VAS recordings were collected for three days each at baseline and after six months of LCIG treatment.

The instruments AIMS and RDRS were used to rate the severity of dyskinesia in the neck, trunk, or limbs (AIMS) or the overall impairment (RDRS) when performing seven set tasks, such as drinking a glass of water or walking five meters. Four tasks were rated using the AIMS, while three tasks were rated on the RDRS. Ratings were made in both “off” and “on” during standardized levodopa tests. For the levodopa tests, the patients were off medication for 12 hours overnight and were then assessed in “off”. The patients were then given their medications (200 mg levodopa or 1.5 times the usual morning dose) and after one hour new assessments were made in “on”. Furthermore, the self-assessment UPDRS items 32 (dyskinesia duration) and 33 (dyskinesia severity) were used to assess dyskinesia. The PDQ-39 was used for assessment of the health-related quality of life. The UPDRS was used to investigate effects on non-motor symptoms (part I) activities of daily life (part II), motor function (part III) and motor fluctuations (part IV). Part III was performed in “off” and “on” during the levodopa test. Participants were instructed to report adverse events whenever such arose. The nonparametric Wilcoxon signed-rank test was used for intra-individual comparisons between baseline and follow-up.

**Results**

The study included nine patients with a median (1<sup>st</sup>-3<sup>rd</sup> quartiles [Q1-Q3]) age of 66 (61-68) years. The median (Q1-Q3) disease duration was 12 (10.5-17) years and the Hoehn & Yahr staging scale (H&Y) in “on” was 2 (1.5-3). All nine patients remained in the study until the six-month follow-up.
The median (Q1-Q3) time in “on with troublesome dyskinesia” decreased from 5.3 (4.7-8.5) h to 2.7 (1.4-4.7, P = .015, Figure 5) h and the time in “on without troublesome dyskinesia” increased from 5.3 (4.7-7.4) h to 13 (12-13.7, P = .008) h between baseline and after six months of treatment. However, one patient reported an increase of “on with troublesome dyskinesia” from 5.7 to 7.3 h per day. The median (Q1-Q3) dyskinesia intensity VAS score decreased from 22.4 (14.6-32.5) to 2.2 (0-4.3; P = .008) and three patients reported no dyskinesia at all after six months of treatment. Significantly less dyskinesia was seen during a levodopa test after six months of treatment as measured on the AIMS (median 9.7 [Q1-Q3: 6.5-11.9] vs. 2.3 [0.4-4.4], P = .008) and the RDRS (1.8 [1.2-2.0] vs. .3 [0-1], P = .008).

**Figure 5.** Hours per day spent in “on with troublesome dyskinesia” at baseline and after 6 months of levodopa-carbidopa intestinal gel infusion. P = .015.

| Table 2: Median UPDRS scores at baseline and after six months of LCIG treatment |
|-------------------------------|-------|-----------|------|
| Instrument part |            | Baseline | Six months |    |
| UPDRS part II, “off”     | 28 (22.5-30.5) | 19 (17.5-24) | .008 |
| UPDRS part II, “on”      | 11 (5-13.5)   | 3 (1.5-5.5)  | .008 |
| UPDRS part III, “off”    | 48 (35-67.5)  | 41 (35-49.5) | .058 |
| UPDRS part III, “on”     | 19 (8.5-36)   | 11 (6-17.5)  | .011 |
| UPDRS total, “off”       | 85 (74-114)   | 62 (57-85.5) | .008 |
| UPDRS total, “on”        | 44 (31.5-68.5)| 21 (14-32.5) | .008 |

UPDRS, Unified Parkinson Disease Rating Scale; LCIG, levodopa-carbidopa intestinal gel. UPDRS part II is a patient-reported evaluation of activities of daily living, while UPDRS part III is a clinical evaluation of motor symptoms.
The median (Q1-Q3) scores on the UPDRS self-assessment items 32 (dyskinesia duration; 2 [1.5-2] vs. 1 [0-1]; P = .014) and 33 (dyskinesia severity, 2 [2-3] vs. 0 [0-1.5], P = .010) were significantly decreased at six months and all patients reported either an improvement or no change.

The median (Q1-Q3) time in “off” decreased from 6 (4.4-8) h to 2 (0.5-3.5, P = .008) h and the UPDRS II and III scores improved significantly in “on” after six months of LCIG treatment (Table 2). Furthermore, the median (Q1-Q3) PDQ-39 score decreased from 76 (51.5-87) to 23 (13-62, P = .021) points, although one patient reported a worsening from 44 to 63 points. The median (Q1-Q3) daily intake of levodopa equivalent units increased significantly between baseline and last follow-up (1331 [952-1504] mg/day vs. 1996 [1714-3046] mg/day, P = .015).

During the six months of LCIG treatment, one patient reported hallucinations and another patient reported vivid dreams. Local infections at the site of the percutaneous endoscopic gastrostomy in the abdominal wall were seen in three other patients. However, these infections could be handled through improved local hygiene and no antibiotics were used. One patient’s percutaneous endoscopic gastrostomy dislocated twice, but after an endoscopic intervention no further irregularities were reported. Four of the patients reported no adverse events during the study.
Do patients’ assessments of their motor state in the PD Home Diary agree with the simultaneous assessments by an observer?

This was a clinical observation study conducted at the Neurology Research Unit, Skåne University Hospital, Lund, Sweden. The study was part of the VALIDATE-PD study program, which is an international collaboration on the evaluation of symptom fluctuations in advanced PD. Participants were recruited at the Department of Neurology, Skåne University Hospital, or through ParkReg.

Each participant attended one screening visit, one day of PD Home Diary (“the Diary”) recording at home, and two office-hour days at the Neurology Research Unit (Figure 6). A junior doctor, three research nurses, and I functioned as observers. All observers were certified in the use of the Movement Disorder Society-sponsored revision of the Unified Parkinson’s Disease Rating Scale (MDS-UPDRS), and permission for the use of the MDS-UPDRS was retrieved from the International Parkinson and Movement Disorder Society.

Persons that had a diagnosis of idiopathic PD, were ≥ 30 years old, and had motor fluctuations according to the treating neurologist or on the MDS-UPDRS were potential participants. Participants were not allowed to exhibit any signs of a secondary or atypical Parkinsonian syndrome, be unable to fill in patient questionnaires or diaries, have a Montreal Cognitive Assessment (MoCA) score < 21, or exhibit psychotic symptoms.

The MoCA was used to screen for for cognitive impairment (lower score indicates more cognitive impairment). The MDS-UPDRS was used for characterization of the study population (higher score indicates more PD symptoms). Participants were instructed in the use of the Diary and received written and oral instructions (~10 min) including pictograms on the selectable motor states. No instruction video or concordance threshold was used. Participants were asked to use the Diary for 24 h while at home to get used to the rating and participants were then able to discuss the rating procedure with study personnel before starting the on-site ratings. The home ratings were not used in the analyses presented herein. No participant failed to comply with the Diary ratings.

During the two days on-site, participants were asked every 30 minutes to rise from a chair, walk seven meters one-way, and note their motor state in the Diary, while the observer made an assessment blinded from the participant’s. The observer’s assessment was based on observations during preparation and execution of the seven-meter walk. In between the half-hourly assessments, participants were typically socializing with each other, solving crossword puzzles, playing cards, reading magazines, listening to radio, having lunch, or drinking coffee.
The selectable motor states for participants and observers were identical: “asleep”, “off”, “on”, “on with non-troublesome dyskinesia”, and “on with troublesome dyskinesia”. Unless otherwise noted, “on with dyskinesia” has replaced “on with non-troublesome dyskinesia” and “on with troublesome dyskinesia” in the analyses.

The McNemar-Bowker test was used to test for symmetry of disagreements between the rating procedures, while Cohen’s κ was used to estimate the agreement between the observer and Diary data. The κ was interpreted as follows: .00-.20: slight, .21-.40: fair, .41-.60: moderate, .61-.80: substantial, and .81-1.00: almost perfect agreement. McNemar’s test was used to compare dyskinesia occurrence and severity between observer and Diary assessments.

The Wilcoxon signed-rank test was used for post-hoc comparison of the estimations from the MDS-UPDRS of time spent in “off” and “on with dyskinesia” to the observer and Diary assessments. The effect size of the Wilcoxon signed-rank test was calculated using \( r = \frac{Z}{\sqrt{N}} \).

**Results**

Eighty-one potential participants received written information about the study and 41 (50.6 %) agreed to participate. One participant declined further participation due to undisclosed reasons after the screening visit, while 40 participants completed the study. A slight majority of patients were male (55 %), and the median (Q1-Q3) age was 70 (62-76 years). The median (Q1-Q3) PD duration was 7 (6-12) years and the duration of motor fluctuations was 51 (25-79) months. The median (Q1-Q3) MDS-
UPDRS total score was 45 (30-57) points, while the H&Y stage was 2 (2-3). The most common symptoms of motor fluctuation were nightly “off” (78 %), “wearing off” (75 %), and peak dose dyskinesia (69 %). No participant failed to reach the MoCA cut-off of 21 points, but 45 % of participants scored 22-25 points, which could be indicative of mild cognitive impairment. No participant failed to comply with Diary ratings.

Out of 2,720 expected ratings, 89 (3.3 %) were missing. A total of 1,322 observer and 1,309 Diary ratings resulted in 1,288 complete pairs of ratings. Ratings were distributed between “off” (observer, Diary [16.9 %, 13.9 %]), “on without dyskinesia” (50.6 %, 55.7 %), and “on with dyskinesia” (32.5 %, 30.4 %). There was a significant difference between observers and Diary ratings in the distribution between the different motor states (P < .001), which was also illustrated by a Cohen’s κ of .358.

There was no significant difference in the number of dyskinesia ratings between observers and Diaries (P = .192), but dyskinesia was significantly less often seen as “troublesome” in observer (2.1 %) than Diary ratings (10.9 %, P < .001). The agreement between observers and participants, using observers as the gold standard, ranged from 71.1 % in “on without dyskinesia” to 57.3 % in “off”, and 49.4 % in “on with dyskinesia”.

Using the participants’ estimation of waking hours spent in “on with dyskinesia” from the MDS-UPDRS item 4.1 for a post-hoc analysis, dyskinesia was found to be underreported in the MDS-UPDRS (median 12.5 [Q1-Q3: 6.0-25.9] %) when compared to observer (27.9 [9.6-55.6] %, P < .001, r = -.43) and Diary (22.4 [2.9-58.6] %, P < .013, r = -.28) ratings. There were no significant differences between the estimation of time spent in “off” in the MDS-UPDRS item 4.3 (median 6.7 [Q1-Q3: 0-19.4] %) and neither observer assessment (13.6 [1.7-26.5] %, P = .066, r = -.21) nor Diary ratings (median 3.4 [0-26.3] %, P = .852, r = -.02).
What symptoms are associated with workforce unavailability in working age persons with PD?

This was a cross-sectional registry-based study using data from ParkReg that were registered in Skåne County, Sweden between the years 2012 and 2015.

Patients treated for PD at three neurology outpatient clinics in Skåne County were invited per mail to be registered in ParkReg. Those who accepted were scheduled for an appointment during which they were interviewed and examined by a research nurse during a standardized 20-minute baseline visit. The follow-up visits were conducted in a similar fashion.

ParkReg participants who were < 65 years of age at the time of their latest examination and had recorded employment-related information were included in this study. For participants with multiple ParkReg entries, data from the latest entry was used in the analyses. The study participants were regarded as unavailable in the workforce if they were a) on full-time disability pension or sick leave, b) on part-time disability pension or sick leave and had no further employment, or c) retired.

A series of simple logistic regression analyses were used to separately test each independent variable for association with workforce unavailability. Being available in the workforce was coded as 0 and being unavailable in the workforce was coded as 1. To reduce the number of variables, only variables with a P < .10 in the simple logistic regression models were included in a multiple logistic regression model. The variance inflation factor was determined for each independent variable to evaluate the degree of multicollinearity among the variables in the multiple logistic regression. A variance inflation factor ≥ 10 was regarded as an indicator of multicollinearity. The proportion of variance in the dependent variable associated with the independent variables was evaluated by the Nagelkerke pseudo R². The goodness-of-fit was assessed using the Hosmer-Lemeshow test.

Results

Of the 420 individuals with registered employment-related information, 321 were excluded as they were ≥ 65 years of age at the time of their last visit. A total of 99 persons were included, of whom 60 % were available in the workforce. The median (Q1-Q3) age was 61 (55-64) years and a majority were men (69 %, Table 3).

Participants’ median (Q1-Q3) PD duration was 5.6 (2.2-9.9) and the H&Y was 2 (1-2) in “on”. Dyskinesia (33 %) and “off” fluctuations (34 %) were the most common motor complications, while anxiety (15 %), depression (22 %), mild cognitive impairment (17 %), and sleep disorders (47 %) were examples of occurring non-motor symptoms.
## Table 3. Participant characteristics from study described in paper III

<table>
<thead>
<tr>
<th>Participant characteristics</th>
<th>Total (n = 99)</th>
<th>Workforce availability Available (n = 59)</th>
<th>Unavailable (n = 40)</th>
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<td>Age, years; median (Q1-Q3)</td>
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<td>Dyskinesia</td>
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<td>“Off” fluctuations</td>
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<td>Mild cognitive impairment</td>
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### Employment status*

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<th>Employment status</th>
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<tr>
<td>Sickness benefit, part-time</td>
<td>13 (13.1)</td>
<td>9 (15.3)</td>
<td>4 (10.0)</td>
</tr>
<tr>
<td>Sickness benefit, full-time</td>
<td>6 (6.1)</td>
<td>0</td>
<td>6 (15.0)</td>
</tr>
<tr>
<td>Disability pension, 25 %</td>
<td>5 (5.1)</td>
<td>5 (8.6)</td>
<td>0</td>
</tr>
<tr>
<td>Disability pension, 50 %</td>
<td>10 (10.1)</td>
<td>7 (12.1)</td>
<td>3 (7.3)</td>
</tr>
<tr>
<td>Disability pension, 75 %</td>
<td>3 (3.0)</td>
<td>1 (1.7)</td>
<td>2 (4.9)</td>
</tr>
<tr>
<td>Disability pension, full-time</td>
<td>22 (22.2)</td>
<td>0</td>
<td>22 (53.7)</td>
</tr>
<tr>
<td>Retired</td>
<td>7 (7.1)</td>
<td>0</td>
<td>7 (17.5)</td>
</tr>
</tbody>
</table>

Data are shown as n (%) unless otherwise noted. REM, rapid eye movement. *Each individual may be part of several employment status categories.
Persons who were available in the workforce worked full-time (49%), part-time (46%), or were unemployed (5%). Those who were unavailable in the workforce received, for instance, full-time disability pension (54%), pension (18%), or full-time sickness benefit (15%).

Associations with unavailability in the workforce were assessed through a series of logistic regression analyses. Significant association with unavailability in the workforce were found for age, PD duration, H&Y, dyskinesia, freezing, “off” fluctuations, and hallucinations and/or psychosis. Age and PD duration exhibited the largest Nagelkerke pseudo $R^2$ (.30 and .18, respectively).

In addition to the significant associations, anxiety and mild cognitive impairment, met the requirement of $P < .1$ in the bivariate logistic regression analyses and were included in a multiple logistic regression model. Although exhibiting a significant association with unavailability in the workforce in the simple logistic regression model, hallucinations and/or psychosis was excluded from the multivariable model due to a low number of cases. Due to missing data for some variables, the multiple logistic regression analysis included 91 participants (of whom 55 were available and 36 unavailable in the workforce). Age (odds ratio [OR] 1.48, 95% confidence interval [CI] 1.18-1.85; $P = .01$), and anxiety (OR 6.81, 95% CI 1.20-38.67, $P = .03$) were found to be associated with workforce unavailability (Nagelkerke pseudo $R^2 = .61$, Hosmer–Lemeshow test $P = .07$).

In order to further investigate the association between anxiety and workforce unavailability post-hoc; sex, depression, and sleep disorders were added to the multiple logistic regression model. However, this did not result in any major changes of the model as seen on the ORs or $P$-values, and neither sex (OR .21, 95% CI .04-1.2; $P = .08$), depression (OR .48, 95% CI .07-3.11; $P = .44$) nor sleep disorders (OR 3.93, 95% CI .84-18.49; $P = .08$) were statistically significant, while the previously significant variables remained so.
Is the sickness absence increased already prior to a first sick-leave episode due to PD?

This was a retrospective longitudinal registry study with a case-control design that used data from the Support for Righteous Sick-leave database (“the database”). The database contains data on all persons in Sweden having been compensated through the national sickness insurance for a sick-leave episode lasting longer than 14 days between years 2008-2014. Sick-leave episodes lasting 14 days or shorter are in Sweden compensated by the employer and are not included in this study. Persons with a first sick-leave episode due to PD were identified and matched to controls (1:1). For the included persons and sick-leave episodes, the database contains data on all previous sickness absence between years 1994-2007, the diagnoses stated in the sickness certification, employment details, education, and income.

The sickness certification diagnoses are coded using the 10th revision of the International Classification of Diseases and Related Health Problems (ICD-10) at the three-character level. Occupations are categorized in accordance with the Swedish Standard Classification of Occupations (SSYK) 1996.

Persons with a first sick-leave episode attributed to PD (incident PD sick-leave cases) were matched by age (exact years), sex, and date of sick-leave to controls with non-PD diagnoses at a 1:1 ratio. An incident PD sick-leave case was defined as an individual with a first sick-leave episode that was exceeding 14 days and was based on the ICD-10 diagnosis code for PD (G20), while a non-PD sick-leave control was an individual with a sick-leave episode that was exceeding 14 days and was based on any other diagnosis than PD.

The ten different occupation categories were dichotomized in two separate ways: first by education (higher education: categories 1-3; lower education: categories 4-9 and 0), then agricultural occupations or not (agricultural, horticultural, forestry, or fishery: category 6; other occupations: 0-5 and 7-9). Differences regarding occupation and employment status between PD sick-leave cases and sick-leave controls at the time of selection were analyzed by fitting occupation and employment data into a multiple logistic regression model. PD sick-leave case/sick-leave control (1/0) was used as the response variable and occupation and employment status as explanatory variables. A \( \chi^2 \) test was used for the post-hoc testing of differences in the prevalence of agricultural occupations between PD sick-leave cases and sick-leave controls.

Paired comparisons between PD sick-leave cases and sick-leave controls of the prevalence of sick-leave episodes exceeding 14 days one, two, and five years prior to the incident PD sick-leave were made with McNemar’s test for dichotomous data. The dichotomizations were made based on whether the person had \( \geq 1 \) sick-leave
episode or not. The Wilcoxon signed-rank test was used to compare PD sick-leave cases and sick-leave controls of the cumulative number of sick-leave days.

Results

A total of 537 incident PD sick-leave cases and 537 sick-leave controls with other diagnoses were identified. A majority of the PD sick-leave cases, as well as controls, were men (63.7%) and the median (min-max) age was 59 (21-67) years. The sick-leave episode that resulted in the person becoming a control was frequently attributed to musculoskeletal disorders (ICD-10 M, 25.9%); injury or poisoning (ICD-10 S or T, 13.8%); and mental and behavioral disorders (ICD-10 F, 12.5%).

Fitting the occupational and employment data into a multiple logistic regression model with case status as outcome variable showed that PD sick-leave cases were less likely to work in occupations with lower education requirements in comparison to sick-leave controls (OR 0.61, 95% CI 0.46-0.80, P < .001). PD sick-leave cases were also more likely to be self-employed or unemployed in comparison to sick-leave controls (OR 2.16, 95% CI 1.28-3.62, P = .004). A post-hoc χ² test found a tendency, albeit non-significant, towards agricultural occupations being more common in the PD group (P = .055).

Using McNemar’s test, a larger portion of PD sick-leave cases than sick-leave controls were found to have had ≥ 1 sick-leave episode one, two, and five years prior to the incident PD sick-leave (P < .001 for each of the three time spans). Moreover, a larger portion of PD sick-leave cases had ≥ 1 sick-leave episode due to one or more musculoskeletal diagnoses one (P = .001), two (P = .036), and five years (P = .006) prior to the incident PD sick-leave compared to the sick-leave controls. No significant difference in the portion of persons with ≥ 1 sick-leave episode due to mental and behavioral diagnoses were seen between PD sick-leave cases and sick-leave controls neither one, two, nor five years prior to the incident PD sick-leave.

Regarding number of total days on sick-leave, using Wilcoxon signed-rank test, PD sick-leave cases were found to have had a higher number of total days on sick-leave than controls one (P < .001), two (P < .001), and five years (P = .001) prior to the incident PD sick-leave. The number of sick-leave days due to musculoskeletal diagnoses were significantly higher among PD sick-leave cases than sick-leave controls one (P = .009), two (P = .023), and five years (P = .033) prior to the incident PD sick-leave. For mental and behavioral diagnoses, no significant differences were found between PD sick-leave cases and sick-leave controls regarding the number of days spent on sick-leave during either of the three studied time spans.
Discussion

RESULTS AT A GLANCE

The overarching aim of this thesis was to increase the knowledge on how health services can support persons with PD. More specifically, one of the two main themes of the thesis is motor complications and the aim was to contribute to a better understanding and utilization of LCIG and the PD Home Diary in the treatment and evaluation of advanced PD. I show that LCIG improves dyskinesia for persons with advanced PD and troublesome dyskinesia, while also improving motor function and health-related quality of life. I also show that the motor state assessments from the PD Home Diary only has a fair agreement with gold standard clinical observer assessments, which warrants a discussion on both the accuracy of the gold standard and the future use of the PD Home Diary.

The other main theme of the thesis is workforce participation and the aim was to improve our understanding of the impact of PD on workforce participation. I show that anxiety was associated with workforce unavailability among working age persons with PD, but this association needs further investigation. I also show that the historical sickness absence is increased among persons that are allowed a first sick-leave due to PD. This was particularly true for historical musculoskeletal sick-leave diagnoses, which could be an effect of prodromal and early PD symptoms.

LCIG AND ITS EFFECTS ON DYSKINESIA

In paper I, our pilot study of nine patients with advanced PD and troublesome dyskinesia, we wanted to investigate the effects of LCIG treatment on dyskinesia. Our main findings were that the median time in “on with troublesome dyskinesia” was decreased from 5.3 to 2.7 h per day (P = .008), while the median time in “on without troublesome dyskinesia” was increased from 5.3 to 13 h per day (P = .008) between baseline and after six months of treatment. The median scores improved significantly on all used scales for measurement of dyskinesia and significant improvements were seen on the UPDRS and the PDQ-39. Furthermore, we observed significant reductions in the time spent in “off”.

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At the time of the original publication of *paper I*, there were several, mostly pre-clinical, studies that had investigated the pathophysiological mechanisms that result in dyskinesia and motor complications in PD. There were both pre-clinical and clinical data that seemed to demonstrate that a treatment based on continuous dopaminergic stimulation might decrease the risk for developing dyskinesia. Continuous dopaminergic stimulation had been shown to have a positive effect on long-term pathophysiological changes through normalization of receptor sensitivity. It is possible that these long-term changes explain the reduced UPDRS score seen also in “off” after six months of LCIG treatment in *paper I*.

Since *paper I* was published, several other studies have supported and elaborated on the effects of LCIG on dyskinesia. A European registry study with a two-year follow-up including 356 participants demonstrated significant reductions in the duration and disability of dyskinesia after initiation of LCIG. This improvement was sustained throughout the two-year study period for those on LCIG monotherapy, but participants with additional PD medication did not see sustained improvement of dyskinesia beyond the first year of LCIG treatment. In a post-hoc analysis of two studies on LCIG that were negative regarding the effect on dyskinesia, participants that spent ≥ 1 h per day in “on with dyskinesia” at baseline were analyzed separately and were found to improve significantly after initiation of LCIG treatment, which is akin to the findings from our study. Recently, two studies have used another instrument, the Unified Dyskinesia Rating Scale, to evaluate the effect on dyskinesia after initiation of LCIG and have presented positive results. With the latter study being a randomized study with open-label controls, the evidence strength for the efficacy of LCIG on dyskinesia has continued to build.

About ten years prior to *paper I*, one study demonstrated how continuous subcutaneous apomorphine infusion reduced dyskinesia in persons with PD. If anything, our study implies that LCIG could have an even better anti-dyskinetic effect than apomorphine infusion as seen on the greater improvements on the AIMS, RDRS, and VAS. However, due to the differences between that study and ours, it is problematic to use them to draw any far-reaching conclusions on the difference in the treatment methods’ effects on dyskinesia. There have been more recent attempts to compare the effects of LCIG and subcutaneous apomorphine infusion, as well as all three device-aided treatments in an observational open-label setting. The latter study does not present data detailing the specific effects on dyskinesia, but shows significant improvement of motor complications as measured by UPDRS part IV after initiation of either of the three treatments. The presented effect size is large for DBS and LCIG and moderate for apomorphine infusion.

As the dose of levodopa is correlated to the occurrence of dyskinesia, it is noteworthy that in our study, the daily levodopa equivalent unit intake increased significantly over the six months following the switch to LCIG treatment, but dyskinesia was nonetheless significantly decreased. Particularly stimulation of dopamine receptor D1 is seen as a driving force behind levodopa-induced
dyskinesia, but levodopa is not the sole culprit. Animal models of levodopa-induced
dyskinesia exhibit increased glutamatergic corticostriatal transmission and
levodopa conversion to dopamine in serotonergic neurons, but also changes in
cholinergic, opioid, histaminic, adrenergic, and cannabinoid pathways. The
continuous dopaminergic stimulation evidently allows for higher doses than oral
treatment without the same side-effects. The decrease in dyskinesia despite
increased levodopa dosages could thus imply that the conventional, pulsatile
distribution of levodopa is the most important cause to dyskinetic complications,
despite the co-existence of other signaling abnormalities. Another partial reason
for the increase in levodopa equivalent units could be that the calculation of
levodopa equivalent units is not an infallible method for standardization of anti-
parkinsonian drugs. However, the algorithm for a now more established method for
calculation of levodopa equivalence, by Tomlinson et al., is very similar to the one
used in our study.

We found that the scores on the UPDRS were improved in “on” after six months of
treatment. This is an indication of an improved quality of the “on” state when
switched from oral and transdermal treatment to LCIG. A reduction of dyskinesia
could lead to better motor function and thus an improvement of UPDRS scores.
UPDRS scores, particularly UPDRS II, are also positively affected by the decreased
duration and improved quality of the time in “off”.

In our study, the median PDQ-39 score decreased significantly after six months of
LCIG treatment. This finding is consistent with earlier studies showing
improvements in health-related quality of life in PD patients on LCIG treatment.
The PDQ-39 score improved substantially for seven of the nine
participants in our study and it can be assumed that these participants have
experienced a real improvement in the health-related quality of life since starting
LCIG treatment. Several studies have investigated whether dyskinesia affects the
patients’ PDQ-39 scores and have found that there are negative effects on at least
the subcategories activity of daily living, cognition, and stigma. Thus, it is
possible that the reduction of dyskinesia has contributed to the improvement of
health-related quality of life in this study, but it is also likely that other factors such
as the reduction of time in “off” and a reduction of non-motor symptoms had an
even greater influence.

We found it noteworthy that the patient whose PDQ-39 score worsened was the
patient with the longest disease duration, hallucinations, and a decrease in levodopa
equivalent units after six months of LCIG. Hence, it is important to consider which
PD patients that are suitable for LCIG treatment and to evaluate the effect for each
individual patient after a few months of treatment. In cases where the health-related
quality of life has worsened after initiation of LCIG treatment, it is reasonable to
question whether the treatment should continue or not. LCIG is not only costly, but
also an invasive treatment with a non-negligible risk for device-related adverse
effects and the benefit to the patient needs to be evaluated continuously.
The effect of LCIG on dyskinesia differed between participants in our study and not everyone improved, which is consistent with the clinical experience of the treatment. There are some persons with advanced PD whose dyskinesia do not improve from treatments based on continuous dopaminergic stimulation. This seems to be especially true for persons who do not exhibit any periods of “on without troublesome dyskinesia” at all under oral and transdermal treatment. This may be a category of patients for whom DBS would be a more suitable treatment. One recent study investigated this closely and looked at baseline characteristics that could lead to worse dyskinesia-related outcomes after initiation of LCIG treatment.92 They found that biphasic dyskinesia while on baseline medication generally improved with increased levodopa doses during LCIG treatment. However, a mix between both peak-dose and biphasic dyskinesia at baseline was particularly detrimental and increased the risk for worse treatment outcomes, biphasic-like dyskinesia also during LCIG, and ultimately, treatment dropout. Biphasic dyskinesia is a well-known phenomenon of advanced PD, but it has only lately been reported to occur during LCIG treatment.93 In retrospect, I cannot determine whether this new knowledge could potentially have changed the outcome for any of the patients in our study that did not improve over six months of LCIG treatment. Going forward, it is clear that an increased vigilance for biphasic dyskinesia has the potential to lead to improved outcomes for a subset of patients as the adjustments needed differ from those experiencing primarily peak-dose dyskinesia.

In our paper I, we saw few serious adverse events over the six months of follow-up. A significant part of the complications that arose were related to the percutaneous endoscopic gastrostomy, which is a pattern that is seen in other studies. One large meta-analysis shows that 76% of persons on LCIG treatment experience some kind of procedure- or device-related adverse event and 17% a serious adverse event.94 As 89% of patients in the randomized controlled trial on LCIG experienced some complication related to the device or tube,24 there is an urgent need for procedural and technological improvements to further improve LCIG treatment.

There are several limitations to the study that need to be considered when interpreting the results; particularly the small sample size and the absence of a control group, a placebo control, and blinding has to be taken into regard. Furthermore, paper I relies on a combination of patient-reported instruments, motor state assessment diaries, and observer ratings. It is a strength that we performed standardized levodopa tests and show that less dyskinesia was produced during the tests after six months of treatment, which indicates that some of the pathophysiological changes inducing dyskinesia have been reversed. More recently, similar studies have started to include data from mobile health technologies such as wearables and smartphone app-based solutions as an exploratory outcome measure, which has the potential to complement participants’ diary assessments. The
potential benefit and caveats of motor state assessment diaries and, to some extent, mobile health technology assessments are discussed in the next section.

LCIG can now be considered a suitable alternative for treatment of dyskinesia in persons with PD and motor complications. Our results were exploratory and included a small number of participants but confirm and strengthen earlier indications on a reduction of dyskinesia during LCIG treatment. Our results also confirm the results from previous studies concerning the reductions of time in “off” and improvement of health-related quality of life after initiation of LCIG treatment.

THE DIARY AND MOTOR STATE ASSESSMENTS

In paper II, our clinical observation study including persons with PD and motor fluctuations, we wanted to investigate the agreement between observer assessments and PD Home Diary ratings. The primary finding of the study was that the agreement between simultaneous observer and Diary assessments of the participants’ PD motor state can be characterized only as fair. Furthermore, we found that as few as 49.4% of Diary ratings in observed “on with dyskinesia”, 57.3% in observed “off”, and 71.1% in observed “on without dyskinesia” were in agreement with the simultaneous observer assessment.

There were some initial efforts to validate the Diary, but not through comparison to an experienced observer which was the focus of paper II. As the Diary and observer data was nominal, Cohen’s κ was chosen over other possible methods for studying validity, such as Pearson or Spearman correlation. The fair agreement between observers and participants (κ = .358) indicates that there often were conflicting assessments of the participant’s motor state. Participants were most successful at recognizing “on without dyskinesia” and least successful at recognizing “on with dyskinesia”. The “off” state is, although an artificial concept, arguably the most clearly defined motor state of the Diary options. However, the motor “off” state is likely to overlap with other sensations of being “off” that are not noticeable to an observer. Persons with PD and motor fluctuations often experience fluctuations of neuropsychiatric, sensory, and autonomic symptoms. These non-motor fluctuations are not necessarily synchronized temporally with the motor fluctuations and it is possible that the occurrence of non-motor fluctuations could have influenced the Diary ratings.

Patients often prefer dyskinesia to experiencing hypokinesia and the clinical impression is that people close to the patient, such as family members and friends, are more likely to notice—and be troubled by—mild dyskinesia than patients themselves. We did not find any significant difference in the number of “on with dyskinesia” ratings between Diary and observer (P = .192) and cannot, based on our
findings, support the notion that the observers more often noticed dyskinesia. Instead, we found that participants rated dyskinesia as “troublesome” more often than observers (P < .001). We refrained from further analysis regarding dyskinesia severity as it is an inherently subjective dichotomization. It is noteworthy that in observed “off”, “on with dyskinesia” made up 17% of Diary ratings, which indicates a lacking understanding among participants about the PD motor states’ characteristics.

During post hoc analysis, we found dyskinesia to be underreported in the MDS-UPDRS item 4.1, but the time spent in “off” estimated in MDS-UPDRS item 4.3 did not significantly differ from the observations. The MDS-UPDRS items 4.1 and 4.3 can be seen as a more direct way to gather the same information gathered in the Diary—time per day spent in “off” or with dyskinesia over the last week—but with significantly less work. However, the items are highly susceptible to recall bias and are dependent on the responder’s understanding of the PD motor states based on a short description included in the instrument. Although this is an interesting exploratory finding, our on-site ratings did not include the nighttime, during which especially “off” is common, and further investigation is warranted.

There are now several mobile health technology solutions that have been developed with the specific aim of assessing motor function in PD. With longitudinal information on motor function, these wearables or app-based solutions could hypothetically fill the same function as the Diary. While many are still in development, others have already started to become established as tools both in the clinical practice and trials.102 Although the potential value of the information gathered by these technical solutions is undeniable, they are currently insufficiently validated and the output is thus difficult to value in comparison to other, more established sources of information on the patient’s motor state. However, the Movement Disorders Society Technology Task Force claims that an imperfect correlation between these new mobile health technologies and the existing gold standard could be justified, or even an asset, as they have the potential to be less subjective and measure domains that are complementary to those of the existing clinical instruments.103 That might certainly be true, but as for the Diary and observer assessments, the general difference between the two assessments first needs to be clarified before the information on that additional domain can be extrapolated (Figure 7). Otherwise, there is a significant risk for misinterpretation of findings and an implied false equivalence between outcome measures, which has now long been the case for the Diary and a motor state assessment by an expert.

The gold standard also deserves to be questioned. The gold standard is by no means perfect, but it is by definition something tried and trusted to which other things can be compared and “merely denotes the best tool available at that time to compare different measures”.104 The often used misnomer “golden standard” also tends to give the gold standard an undeserved air of excellence. In the setting of paper II, the argument could be made that an instrument similar to the patient-reported Diary
Figure 7. Reasons for variations in the motor state assessments as exemplified by the “off” state. A = Diary "off", but not observed "off". The result of either 1) misclassification by participant, or 2) the participant experiencing non-motor dimensions of “off” that influence the rating but are not visible to the observer. Some variation can be ascribed to the expected difference between two independent raters. B = Diary and observed "off". Agreement between participant and observer on the participant’s motor state. Very likely to be true motor “off”. C = Observed “off”, but not diary “off”: Likely to be true motor “off”. The result of either 1) misclassification by the participant or 2) the lacking of non-motor symptoms that are identified by participant as central to the experience of being "off". Some variation can be ascribed to the expected difference between two independent raters.

should be the new gold standard for assessment of the PD motor state, as the increased focus on patients’ experiences would be in line with the current trends towards patient-centered care. However, this would be a significant change and warrants further discussion. Studies of new mobile health technologies should therefore include parallel comparisons to both Diary and observer assessments to increase our knowledge of the similarities and differences between the modes of measurement.

The study in paper II has several limitations. Firstly, all observers had experience of PD and were certified in the use of MDS-UPDRS, but were not Movement Disorder Specialists and could thus be considered less accurate than the current gold standard. Furthermore, using multiple observers may have influenced the results and no calculations of the inter-rater reliability between observers were performed (such as the Fleiss’ κ). However, a parallel German cohort with a similar protocol used a single rater, a physiotherapist with experience from working with PD, and the findings from that study are in most aspects in agreement with the results in our paper II.105 Lastly, the participant instructions for the use of the Diary could have been more rigorous and included the recommended instruction video,30 which might have increased the agreement with observer assessments. However, our assessment
is that the level of instructions to participants in this study was representative of how the Diary is used in clinical trials and in clinical practice.

In addition to providing guidance for implementation of mobile health technologies, the Movement Disorders Society Technology Task Force has identified a number of limitations among the currently available PD patient diaries and proposed a comprehensive development plan for a new eDiary. An eDiary is certainly warranted, but the Diary used in papers I and II is likely to remain a mainstay in clinical trials for several years to come. Based on our findings, and if observer assessments are held as the gold standard, the Diary does not seem to be an accurate depiction of the patients’ motor state. However, that does not imply that the Diary is not a useful tool. The Diary should still be regarded as an important patient reported outcome, albeit a composite that is likely to be influenced by other factors of the patient’s experience than strictly the observed motor state.

**PD IN THE WORKFORCE**

*Historical Sickness Absence: PD in Disguise?*

In the search for disease modifying treatment for PD, it is becoming increasingly evident that interventions need to start early as the disease process is already far along at the time of a PD diagnosis. There is no reason to think that the situation is any different when it comes to workforce participation; daily functioning is starting to be affected years prior to the diagnosis, indicating that interventions aiming to support workforce participation needs to be a priority early on. By using retrospective workforce participation data preceding an incident PD sick-leave, we saw an opportunity to improve our understanding of what is likely to be clinically relevant early symptoms related to the PD process.

The primary finding from paper IV is that persons who later were allowed sick-leave due to PD were more absent from work due to illness than matched sick-leave controls already five years prior to the incident PD sick-leave episode. More specifically, we found that persons later diagnosed with PD had been more absent from work with reference to musculoskeletal diagnoses one, two, and five years prior to the incident PD sick-leave episode, while there was no increase in sickness absence with regards to mental and behavioral diagnoses.

The finding that persons with PD exhibit increased pre-diagnosis sickness absence due to musculoskeletal disorders is not previously unheard of; a study from secondary care in Denmark reported that musculoskeletal diagnoses in general—and lumbar pain in particular—are more common among patients that three years later receive a PD diagnosis than among those that do not. Similar findings based on data from primary care have also been presented. Pain is a non-motor symptom.
that is common during the prodromal phase of PD.\textsuperscript{109-111} It is possible that an increased occurrence of pain is a partial explanation of the increased sickness absence due to musculoskeletal diagnoses in the present study. Furthermore, the occurrence of tremor, fatigue, dizziness, shoulder pain or stiffness, balance impairments, rigidity, and hypotension are overrepresented in persons two to ten years prior to a PD diagnosis,\textsuperscript{109} factors that either on their own or indirectly could result in sickness absence due to musculoskeletal diagnoses. By studying a cohort of persons with rapid eye movement sleep behavior disorder, which has a very high conversion rate to PD, it has been shown that subtle motor signs started to appear already 4.5 years prior to the point at which a PD diagnosis could be made.\textsuperscript{112} This is possibly indicative of the same tendency for an early decrease in motor function that is captured also in my paper IV, albeit under another label: musculoskeletal sickness absence.

At the time for the analysis of the data in paper IV, we had already seen an association between anxiety and workforce unavailability in paper III. The hypothesis was therefore primarily that there would be an association between prior mental and behavioral sickness absence and a subsequent PD sick-leave. Instead, there were no differences regarding mental and behavioral diagnoses between the PD sick-leave cases and sick-leave controls in the present study. Anxiety, together with depression and anhedonia, are known to be common from an early stage of the disease process and are all among the non-motor symptoms that are regarded as part of the prodromal phase of PD.\textsuperscript{59, 113, 114} There are several possible explanations to the discrepancies between the present and previous studies. Comorbidity with musculoskeletal and mental health issues are common in people with PD and it is possible that physicians chose to use the less stigmatizing—i.e. musculoskeletal—diagnosis on the sickness certification form when confronted with both somatic and psychiatric illness. Our study also included persons who had received a sickness certification from a physician at any level of the health care system and did not only involve persons diagnosed in hospital care.\textsuperscript{108} This difference in the selection of the study populations could contribute to the discrepancies between the findings. Research on depression and mental health issues in PD is further complicated by the fact that neither PD duration, stage, severity, or age of onset is consistently associated with the occurrence or severity of depressive episodes in PD.\textsuperscript{115} However, the retrospective design of this study does not permit drawing conclusions about causal mechanisms, implying that more research on comorbidity between mental and behavioral disease and PD is warranted.

Sleep disorders, in particular rapid eye movement sleep behavior disorder, are common from an early stage of the PD process and have been shown to be important contributors to a worsened quality of life.\textsuperscript{116} A sleep disorder per se is unlikely to result in any longer sickness absence episodes that would lead to inclusion in our paper IV, but sleep disorders are likely to be a common comorbidity among participants in the study. Insomnia and short sleep duration among non-PD patients
with psychiatric disorders is known to be associated with both impaired work performance and long-term absenteeism. Although a plausible causal chain of events linking sleep disorders and workforce exit could be constructed also in PD, I found no significant evidence for a connection between the two in my papers III and IV. The study in paper III was likely underpowered to do so even if there were a difference, while the study in paper IV was not designed to specifically investigate sleep disorders. Other study designs are likely to be more effective at investigating the effects of sleep disorders on workforce participation in early PD, particularly cohort studies of persons with rapid eye movement sleep behavior disorder would be better equipped.

There are several limitations to our investigation into the sickness absence prior to a PD sick-leave in paper IV that need consideration. In Sweden, the employer compensates the employee during the first 14 days of a sick-leave episode, and a physician’s certificate with a diagnosis is only required after day seven. Thus, reliable diagnoses for sick-leave episodes lasting 14 days or less are not systematically available and were therefore not included in the analyses. This means that common, but more trivial, short sick-leave episodes due to for example infections or less severe reactions to stress are not included in this study. Furthermore, the control group was likely to have more health problems than the general population, which could lead to a relative underestimation of the illness burden in the PD group compared to the general population. Lastly, we have no data on the dates of PD diagnosis in the study sample, and no information beyond the clinical experience of how the date of diagnosis relates to the first sick-leave episode attributed to PD.

Our hypothesis that the PD process sometimes enters the scene in the disguise of a musculoskeletal disorder can of course be problematized. PD is heterogeneous and so is the prodromal stage of the disease process. A recent review suggests a number of ways to subtype prodromal PD in addition to a rapid eye movement sleep behavior disorder subtype: body-first and brain-first subtypes, genetic subtypes, and more speculatively, biological subtypes. It is possible that each of these subtypes has a typical phenotype and thus wears one of several disguises: be it the constipation and sleep disorder of the body-first subtype, hyposmia of the brain-first subtype, or muscle rigidity of the LRRK2 mutation genetic subtype.

The results of paper IV suggest that non-trivial sickness absence is increased among persons with PD when compared to controls at least five years prior to the first sick-leave episode ascribed to PD, both in terms of total sickness absence and in sickness absence due to musculoskeletal diagnoses. No specific increase was detected for mental and behavioral diagnoses, but this was in comparison to a control group that was likely more prone to sickness absence than the general population. The studying of sick-leave history among persons with PD is an opportunity to increase the knowledge about the disease process per se and could be an interesting addition to the now growing number of cohorts of patients with prodromal PD. Although
intervention during the prodromal stage of PD is currently unfeasible outside of a study setting, our results point to the need for interventions addressing workforce participation issues soon after diagnosis as the decline in work ability may have started several years earlier.

Modifiable Factors of PD and Workforce Unavailability

PD has historically prevented workforce participation, but with the improved treatment options that are now available, there is hope for and a need to sustain workforce participation also after diagnosis. In the exploratory cross-sectional registry study from paper III, we sought to contribute to the limited knowledge base regarding factors associated with workforce unavailability among people with PD. Our primary finding was that experiencing anxiety was associated with being unavailable in the workforce. Moreover, no significant associations could be established for factors such as sex, motor fluctuations, depression, or sleep disorders.

When interpreting the results, it is important to consider that the study design does not allow for interpretations of causation or determination of predictive factors. Therefore, it must be noted that anxiety could be an effect of rather than a cause for being unavailable in the workforce. There is, however, some support for the notion that anxiety has a role in the process causing workforce unavailability. The studies are relatively few and far in between, but there is one prospective study of people with PD who were employed at baseline that shows that those who subsequently left the workforce also experienced more anxiety at baseline. However, that finding was no longer significant after adjusting for age, sex, and disease duration. Furthermore, associations between anxiety and early retirement have been found in non-PD populations and anxiety has also been reported to predict permanent disability in a large German study on a non-PD population based on health insurance data. A study on 287 working age American veterans shows that both depression and anxiety seem to constitute barriers to employment, job search self-efficacy, and work performance, which could be indicative of anxiety as a cause for the reduced workforce participation.

The stabilization of motor complications has been hypothesized to lead to less work absenteeism in people with PD. In our study in paper III, “off” fluctuations, freezing, and dyskinesia were associated with workforce unavailability in the simple logistic regression analyses, but did not remain significant in the multiple logistic regression analysis. Dyskinesia might not always affect patient-reported overall health-outcomes negatively, but it may signal illness and is thus plausible to increase stigmatization in a work environment. This is supported by the finding that dyskinesia, as previously discussed in the context of levodopa infusion, can have a detrimental effect on activities of daily living, cognition, stigma, and bodily discomfort, which all appear relevant to most occupations. We found it noteworthy that in this study, “off” fluctuations did not seem to be associated with workforce
unavailability. One possible explanation might be that participants with for example foreseeable time in “off” in the morning or wearing “off” during the afternoon were able to adjust their working hours and/or medication; thus limiting the effect of “off” fluctuations on the ability to work. It is also very likely that it is not only the duration, but also the “off” symptom severity that influence the impact of “off” fluctuations on a person’s ability to work. However, no data are available regarding “off” phase symptom severity in the sample included in paper III, which appears to represent relatively mild PD.

There were noteworthy differences between the simple and multiple logistic regression models in paper III. Several factors only exhibited significant associations to unavailability in the workforce in the simple logistic regression models. For instance, PD duration was not significantly associated with unavailability in the workforce in the multiple logistic regression model, despite an almost twice as long median duration in the group of persons who were unavailable compared to those who were available in the workforce. It is nonetheless possible that when also taking specific symptoms and complications into consideration, the importance of the PD duration is reduced considerably. For several of the other symptoms and complications, a larger sample size would have increased the number of cases and could thus have helped nuance the differences between the simple and multiple logistic regression models. Moreover, H&Y was dichotomized due to both the small sample size and the fact that a vast majority of participants were in the earlier H&Y stages. Although this dichotomization resulted in a loss of information, the cut-off was selected in order to create two similarly sized groups for the analysis and to enable us to capture early differences in motor symptoms.

Two important factors of work ability that are not PD symptoms but modifiable are work tasks and competence (Figure 3). The interplay between symptoms and type of occupation may influence the likelihood of being able to continue working or getting sick-listed. There are also differences between occupations with regard to whether a specific symptom becomes limiting in the execution of work tasks. It is not a given that a person should or must continue in the same occupation after a PD diagnosis as there are occupations and work tasks that are likely to be a bad fit even though the person could perform other work tasks. As discussed earlier, it has been difficult to establish whether persons with blue- or white-collar work are more likely to continue working after a PD diagnosis—likely due to the imprecise and arbitrary dichotomization. In our paper IV, we found that individuals in the PD group were less likely to be involved in manual work. It is possible that this difference is caused by a gradual increase of symptoms, which influences the selection of occupation, or may be attributed to shared personality traits among persons with PD. Furthermore, the observed tendency (post-hoc χ² test, P = .055) for agricultural occupations to be more common in the PD group corresponds with the notion that pesticide exposure could be a risk factor for PD, however, the design and size of
this study does not allow for any conclusions regarding these occupational differences.

The decision to leave one’s employment is a major life event and may depend on factors not directly related to PD, such as social support, family life, personal interests, and hobbies. It is therefore important that patients have access to the support and information needed to make an informed decision on leaving or continuing their employment. Although we hypothesize that some workforce participation could be beneficial for many individuals with PD, work perceived as beyond one’s capacity is evidently associated with life dissatisfaction. This further emphasizes the importance of planning, communication with the employers and considerations of possibilities for adjustments of work tasks, hours and environments. Although further longitudinal studies are needed in order to investigate cause and effect, the present findings suggest that one should address anxiety in order to help promote workforce participation; including both pharmacological and non-pharmacological interventions.

There are a number of limitations that need to be considered when interpreting the results from our paper III. Firstly, the multiple logistic regression model was based on a limited sample size. Moreover, some of the included variables were captured using coarse indicators and symptom severity was not assessed. Several variables not studied here may also be of importance, particularly fatigue, walking difficulties, and falls. Fatigue has more often been regarded as one of the most distressing symptoms by employed compared to non-employed people with PD. Unfortunately, no information on fatigue has been registered in ParkReg. Furthermore, at the time of publication of our paper III, Swedish pension benefits could be drawn from the month a person turned 61 years old, although people were entitled to continue to work up to an age of 67. For persons receiving disability pension, the disability pension was replaced by retirement pension when the person turns 61 years old. This means that the participants of this study who were retired (7 %) may have been so either by choice or after receiving disability pension up until he or she turned 61 years old. ParkReg was relatively new at the time of the study but as of October 2021, the Skåne county part of the registry has continued to expand and now contains information on more than 1,500 persons with PD. As a result, the registry is now likely to be a more accurate representation of the Skåne county PD population.

Based on paper III, anxiety is associated with unavailability in the workforce in persons with PD. As a potentially modifiable factor, it could be possible to target anxiety for future interventions aiming at increasing workforce participation in persons with PD. However, further studies are needed for a better understanding of factors contributing to workforce unavailability. Particularly studies with larger samples and longitudinal data are warranted to investigate if there is not only association but causation in the found connection between anxiety and workforce unavailability.
FUTURE PERSPECTIVES

Treatment and Evaluation of Motor Fluctuations and Dyskinesia

The new knowledge on LCIG and dyskinesia provided by paper I has now already been expanded upon, but there is still much left to explore. A randomized study of the device-aided treatments in patients with particularly troublesome dyskinesia would be interesting, but is unlikely. Biphasic dyskinesia has just recently been recognized to occur also during LCIG treatment and more investigation into strategies for how to effectively adjust the LCIG treatment after the clinical response is warranted. Lastly, a new generation of treatments aiming for continuous dopaminergic stimulation is likely to soon be available in clinical practice. This calls for a new discussion on the device-aided treatments and for whom, when, and how these treatment options should be made available to persons with PD.

The place for device-aided treatment such as LCIG in the prevention of workforce unavailability in PD still remains to be made clear, but there are some early indications that device-aided treatment helps sustain the work ability. However, it is likely that the device-aided treatments are currently used at a stage of the disease where the negative effects on work ability are already significant. In this context, it would be of great interest to include workforce participation as an outcome in a trial on early device-aided treatment in PD. Possibly, a new generation of less invasive device-aided treatments could make that study more realistic.

The methods for assessment of the PD motor state and motor function will soon undergo significant changes that have the potential to lead to better patient outcomes. Building on our findings, there are at least two important steps towards securing more useful and accurate PD motor state assessments. Firstly, the influence of non-motor fluctuations on Diary assessments needs to be clarified to improve our understanding of the difference between observed and experienced PD motor states. That is, the motor ratings by the participant might also reflect non-motor fluctuations and this is something that we will investigate further in the collected data from the VALIDATE-PD study program. Secondly, the new mobile health technologies need to be validated in comparison to both Diary and Movement Disorder Specialist assessments before being put to wide use in order to contextualize results. Otherwise, there is a risk that the rapid technical development could result in a significant shift towards intervention against scores without an inherent meaning rather than symptoms that make a clinical difference to patients.

Early Diagnosis and Workforce Participation

Further knowledge about factors useful for early identification of persons with a high risk for developing PD is needed and the development of research criteria for prodromal PD was a significant step. When one or more treatments for PD presumably have been proven being disease-modifying, there will suddenly be a
great increase in the need for early and accurate diagnosis to improve long-term outcomes. Based on our own and previous studies on workforce participation in PD, it is possible to point to several important challenges. Based on our findings, vigilance for early motor symptoms as well non-motor symptoms such as pain could have a place besides screening for combinations of non-motor symptoms such as olfactory impairment, rapid eye movement sleep behavior disorder, and autonomic dysfunction. However, this is likely to have to be combined with biochemical, genetic, and imaging biomarkers to be both sensitive and specific enough. Anxiety and mood disorders have been connected to the prodromal phase of PD, but are just like musculoskeletal disorders common in the general population. The role of psychiatric symptoms in this setting needs further clarification as we did not see any increased sickness absence due to mental and behavioral disorders prior to a PD sick-leave in paper IV.

Although receiving much of the focus in this thesis, the health services is clearly not the only actor of importance beside the person with PD in the strive towards a sustainable working life. As indicated by the large number of actors involved, the rehabilitation process is complex and highly dependent on effective coordination and cooperation. A somber view on workforce participation among persons with PD is that it is a not very highly prioritized issue. The medical treatment needs to be addressed by a team of experienced healthcare professionals which is demanding and require considerable resources that are often not available, while the coordination with employers and the Social Insurance Agency needs further streamlining. Frankly, there is a substantial risk that the issue of workforce participation in PD will not be sufficiently addressed until disease modifying treatment is available. That does not mean that the situation cannot be improved in the short-term. Extrapolating from our knowledge of prediagnostic functioning trajectories, it is also often the clinical experience that a proactive approach should be held towards known symptoms such as daytime sleepiness, motor fluctuations, and reduced stress tolerance from an early stage. The alternative, which is to try addressing the symptoms as we go and only after they have become disabling and obvious to the patient, is not very likely to be successful. Patients often have difficulties identifying symptoms as part of the disease at an early stage and need direct questions in order to narrow down their problems. Therefore, the importance of the multi-disciplinary team cannot be stressed enough as it is a significant asset in these situations where the responsibilities can be shared and patients can receive support on different aspects of the disease from several sources. Although the evidence in support of the multi-disciplinary team is lacking, the clinical experience is that needed interventions are more likely to be both identified and executed at the suitable time through collaboration between the members of the team. The multi-disciplinary team also has the potential to improve interactions and cooperation with other actors outside of the health services, such as the Social Insurance Agency and employers, which must not be underestimated.
There is a slowly moving tendency towards increased acceptance for disability in society, but that acceptance is yet to reach many workplaces. Persons with PD experience stigma and barriers that discourages continued workforce participation after a PD diagnosis. Particularly younger persons with PD seem to be vulnerable to stigmatization and in need of more support to sustain their working ability.\textsuperscript{52} Health and functional capacities are, although important, only one type of factor that has significant impact on a person’s working ability (Figure 3) and the interventions need to have a holistic approach and be synchronized with other actors within and outside the healthcare system. Persons with PD not only encounter a heterogeneous disease, but also heterogeneous working situations. A major obstacle is therefore that we currently do not have any validated instrument for measurement of working capacity among persons with PD. This is a top priority in order to offer working persons with PD targeted support that potentially could reduce some of the psychological, social, and economic ramifications of the disease. A small but useful measure would be to start including information on workforce participation in both new and ongoing longitudinal studies on prodromal and clinical PD as that may help identify symptoms that have a significantly negative effect on work ability.
Conclusions and Implications

With this thesis, I wanted to improve our understanding of two established and now long-used tools in PD treatment and research: LCIG for treatment of advanced PD, and the PD Home Diary for assessment of the PD motor state. I show that LCIG improves dyskinesia in a PD population with significant periods of troublesome dyskinesia at baseline and, as previously shown, that there is a reduction of time spent in “off” at the same time as the health-related quality of life improves. Given the technological and pharmacological advancements, it is difficult to predict what place LCIG will have in the treatment of advanced PD within ten years’ time. Less invasive routes of administration than a gastrostomy is warranted and subcutaneous administration of levodopa is currently investigated in several clinical trials. However, the knowledge now gained on the effects of continuous dopaminergic stimulation is likely to largely carry over to these new potential treatment options.

Accurate motor state assessments are central to the evaluation of treatment effects in PD. I show that the agreement between PD Home Diary and observer assessment is fair at best, which highlights the problem of assuming an approximate equivalence to the gold standard. This discussion has only begun as the technological development is considerable in this field and eDiaries, wearables, and app-based solutions are soon to become part of the new norm for assessment of the PD motor state. There is no doubt that they will become important tools in both the clinical practice and for research purposes, but there is a significant need for proper validation before putting these mobile health technologies to wider use.

Planning this thesis, I also identified two knowledge gaps in current research and clinical practice: what specific symptoms have a particularly negative influence on workforce participation in PD and how does prodromal and early PD affect sickness absence? Involuntary workforce exit is often seen as one of the most negative effects of developing PD. I show here that there is an association between anxiety and workforce unavailability. Anxiety is known to affect work performance and job search efficacy negatively, but there is still much to learn about the association in PD: is it causal and, if so, does anxiety lead to workforce unavailability or vice versa? Longitudinal studies are needed to investigate the association further, but anxiety should nonetheless be addressed in the meantime given the already known negative effects. Early retirement or sickness benefit may in itself have negative side effects and it is important to thoroughly consider the individual working ability and whether there in fact is a medical indication before resorting to that resolution.
Functioning is known to worsen in the years leading up to a PD diagnosis. I show that persons that are allowed a first sick-leave due to PD exhibit a higher retrospective sickness absence over the previous five years in comparison to controls, particularly due to musculoskeletal disorders. Early motor signs are seen in some subtypes of prodromal PD and non-motor symptoms such as pain are likely to result in musculoskeletal sickness absence. There is much to learn on prodromal and early PD and as the field continues to expand, the early effects on functioning, work ability, and workforce participation need more attention.

Now two centuries since the first comprehensive description of PD, we have access to treatments that effectively reduce the disability caused by the disease, but there are still no interventions that result in disease modification. Moving forward, it seems as if the device, diary, and disguise will be central topics of PD research. Device-aided treatment is currently the most reliable method for achieving continuous dopaminergic stimulation and reduction of motor complications in advanced PD, but the current methods needs to be refined. The Diary has been central in the evaluation of clinical trials, but the need for validated methods of measurement of both motor and non-motor symptoms has now been highlighted. Lastly and probably most importantly, the disease process in all of its disguises in prodromal and early PD will continue to receive much attention. It is at that stage that disease-modifying treatments will be of particular benefit to delay the development of early disease signs and the onset of cardinal motor symptoms. Future disease-modifying treatments will in all likelihood lead to a substantial improvement of the socioeconomic impact of the disease, but further efforts to improve the support for working age persons with PD cannot wait.
Sammanfattning på svenska


Noggranna bedömningar av en persons rörlighet är centrala för utvärderingen av effekten av läkemedelsbehandlingen vid Parkinsons sjukdom. Jag valde därför att titta närmare på en särskild form av egenrapporterade patientdagböcker som är
vanligt förekommande i kliniska studier kring Parkinsons sjukdom. Jag visar att patientens bedömning av hur rörlig den är för stunden ofta inte stämmer särskilt väl med en experts bedömning av patienten. Expertens skattning har traditionellt setts som riktmärket, samtidigt som patientdagböckerna har tillskrivits stor vikt i studier. Vi visar här att det kan vara problematiskt att anta att dessa två olika mätmetoder är mer eller mindre synonyma. Det ställs på sin spets då den tekniska utvecklingen är betydande också inom detta område och elektroniska dagböcker, bärbar elektronik (så kallade ”wearables”) och appbaserade lösningar kommer snart att bli en del av den nya normen för utvärdering av rörelseförmågan hos personer med Parkinsons sjukdom. Det råder ingen tvivel om att dessa teknik kommer att bli viktiga både inom kliniken och forskningen, men det finns ett stort behov av att validera dessa innan de kan komma till bredare användning. Precis vad mäter de och hur förhåller sig de resultaten till utfallet av redan etablerade mätmetoder?


Acknowledgments

This thesis was made possible through the kind contributions from study participants, collaborators, and funders. Others have helped shape the thesis through their mentoring, encouragement, and advice.

First of all, many thanks to Per Odin. When I have to choose one of his qualities as a supervisor (with the emphasis on one, not have to), it is his knack for collaboration. His openness and optimistic approach towards past, present, and future colleagues is the main reason for the collaborative and prestigeless spirit in our shared projects.

Thanks to Susanne Iwarsson, Örjan Dahlström, and Mia Nilsson for their expert advice, each from a slightly different point of view than my own, and for being genuinely pleasant and supportive at every step of this process. Thanks also to Peter Hagell and Sven Pålhagen for their generous advice to this then medical student.

Thanks to my clinical mentor Yulia Surova for the support when I am clinically lost. Her eagerness to learn and develop in the professional role is a brilliant example of how this line of work is supposed to be done.

Thanks to my colleagues at the Research Unit: Ulrika Mundt-Petersen, Trinette van Vliet, Kristina Rosqvist, Jeanette Härnberg, Anna Weddig, Monica Scharfenort, Christin Karremo, Gunilla Thorneman, Emma Pettersson, Sofia Christiansson, Frida Jernstedt, Sotirios Grigoriou, Yvonne Olsson, Emil Ygland Rödström, Sara Hall, Andreea Ilinca, Angelina Grönberg, Carin Janz, and many more.

Thanks to Karen and Thomas Fox, Holger Honig, Claas Ehlers, and Matthias von Mering for welcoming me to Bremerhaven, and to Matthias Löhle, Alexander Storch, and Alexander Bremer for an inspiring collaboration in the final stretch.

The author Jonathan Franzen deserves a mention for his novel “The Corrections” (2001) and his creation of Alfred Lambert, a retired railway engineer experiencing the effects of Parkinson’s disease, which contributed to waking my interest in this topic. In a parallel universe, this thesis is on railway engineering.

Finally, thanks to my family, my friends, and to Stella.

Malmö, October 2021
Funding

This thesis was supported by governmental funding of clinical research within the Swedish National Health Services and by Skåne University Hospital Foundations and Donations.
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