# Clinical Predictors of disease progression in Parkinson's disease

Zhu, K.

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Cover design: Kangdi Zhu en Remco Wetzels
Printing: RidderPrint B.V.

The research presented in this thesis was performed at the Department of Neurology, Leiden University Medical Center, The Netherlands.

The publication of this thesis was financially supported by:
- De Parkinson Vereniging
- UCB Pharma B.V.
- Vakgroep neurologen Reinier de Graaf Groep

# CLINICAL PREDICTORS OF DISEASE PROGRESSION IN PARKINSON'S DISEASE

PROEFSCHRIFT
ter verkrijging van de graad van Doctor
aan de Universiteit Leiden,

op gezag van
Rector Magnificus prof. mr. C.J.J.M. Stolker,
volgens besluit van het College voor promoties
te verdedigen op woensdag 22 november 2017
klokke 16:15 uur

DOOR
Kangdi Zhu,
geboren te Wuhan, China
in 1990.

PROMOTOR:
Professor dr. J.J. van Hilten

CO-PROMOTOR:
Dr. J.M. Marinus

LEDEN PROMOTIECOMMISSIE:
Professor dr. R.A.C. Roos
Professor dr. H.W. Berendse, VU Medical Center, Amsterdam, the Netherlands
Dr. A.J.W. Boon, Erasmus University Medical Center, Rotterdam, the Netherlands

Chapter 1:

# The course of non-motor symptoms in Parkinson's disease: An introduction

**Parkinson's disease**

Parkinson's disease (PD) is a complex neurodegenerative disorder that has first been described almost two centuries ago.[1] It is recognised as the most common neurodegenerative disorder after Alzheimer's disease and affects almost two percent of the population over 65 years.[2] Some of the most prominent components of this disease were first described in the 19th century by James Parkinson in his 'Essay on the shaking palsy'.[3] At the time the main features of the disease were considered to consist of bradykinesia, muscular rigidity, and rest tremor.[4] This description was later refined by Jean-Martin Charcot, who noted that PD patients did not necessarily have to present with tremor. In addition, he identified two different subtypes of disease, a tremorous and a rigid/akinetic form.[4,5]

Although age is the greatest risk factor for the development of PD (the prevalence and incidence increase exponentially after the age of 80), research indicates that the disease develops from a complex interplay of genetics and the environment.[1,6,7]

Until recently, the diagnosis of PD was based on the presence of motor symptoms (Table 1.1) that are related to a deficiency of the neurotransmitter dopamine in several regions of the basal ganglia.[8] Recently, however, the criteria have been refined, now also incorporating several non-motor features of PD (Table 1.1).[9]

**Table 1.1:** MDS Clinical Diagnostic Criteria for PD - Executive Summary/Completion Form[9]

The first essential criterion is parkinsonism, which is defined as bradykinesia, in combination with at least 1 of rest tremor or rigidity. Examination of all cardinal manifestations should be carried out as described in the MDS–Unified Parkinson Disease Rating Scale.[8] Once parkinsonism has been diagnosed:

Diagnosis of **Clinically Established PD** requires:

1. Absence of absolute exclusion criteria
2. At least two supportive criteria, and no red flags

Diagnosis of **Clinically Probable PD** requires:

1. Absence of absolute exclusion criteria
2. Presence of red flags counterbalanced by supportive criteria

If 1 red flag is present, there must also be at least 1 supportive criterion. If 2 red flags, at least 2 supportive criteria are needed. No more than 2 red flags are allowed for this category.

**Supportive criteria**

1. Clear and dramatic beneficial response to dopaminergic therapy. During initial treatment, patient returned to normal or near-normal level of function. In the absence of clear documentation of initial response a dramatic response can be classified as:
    a) Marked improvement with dose increases or marked worsening with dose decreases. Mild changes do not qualify. Document this either objectively (>30% in UPDRS III with change in treatment), or subjectively (clearly-documented history of marked changes from a reliable patient or caregiver).
    b) Unequivocal and marked on/off fluctuations, which must have at some point included predictable end-of-dose wearing off.
2. Presence of levodopa-induced dyskinesia
3. Rest tremor of a limb, documented on clinical examination (in past, or on current examination)
4. The presence of either olfactory loss or cardiac sympathetic denervation on MIBG scintigraphy

**Absolute exclusion criteria:** The presence of any of these features rules out PD:

1. Unequivocal cerebellar abnormalities, such as cerebellar gait, limb ataxia, or cerebellar oculomotor abnormalities (e.g., sustained gaze evoked nystagmus, macro square wave jerks, hypermetric saccades)
2. Downward vertical supranuclear gaze palsy, or selective slowing of downward vertical saccades
3. Diagnosis of probable behavioural variant frontotemporal dementia or primary progressive aphasia, defined according to consensus criteria[10] within the first 5 y of disease.
4. Parkinsonian features restricted to the lower limbs for more than 3 y
5. Treatment with a dopamine receptor blocker or a dopamine-depleting agent in a dose and time-course consistent with drug-induced parkinsonism
6. Absence of observable response to high-dose levodopa despite at least moderate severity of disease
7. Unequivocal cortical sensory loss (i.e., graphesthesia, stereognosis with intact primary sensory modalities), clear limb ideomotor apraxia, or progressive aphasia
8. Normal functional neuroimaging of the presynaptic dopaminergic system
9. Documentation of an alternative condition known to produce parkinsonism and plausibly connected to the patient's symptoms, or, the expert evaluating physician, based on the full diagnostic assessment feels that an alternative syndrome is *more likely* than PD

**Table 1.1:** MDS Clinical Diagnostic Criteria for PD - Executive Summary/ Completion Form *(continued)*[9]

**Red flags**

1. Rapid progression of gait impairment requiring regular use of wheelchair within 5 y of onset
2. A complete absence of progression of motor symptoms or signs over 5 or more y unless stability is related to treatment
3. Early bulbar dysfunction: **severe** dysphonia or dysarthria (speech unintelligible most of the time) or severe dysphagia (requiring soft food, NG tube, or gastrostomy feeding) within first 5 y
4. Inspiratory respiratory dysfunction: either diurnal or nocturnal inspiratory stridor or frequent inspiratory sighs
5. Severe autonomic failure in the first 5 y of disease. This can include:
a) Orthostatic hypotension[11] —orthostatic decrease of blood pressure within 3 min of standing by at least 30 mm Hg systolic or 15 mm Hg diastolic, in the absence of dehydration, medication, or other diseases that could plausibly explain autonomic dysfunction, or
b) Severe urinary retention or urinary incontinence in the first 5 y of disease (excluding long-standing or small amount stress incontinence in women), that is not simply functional incontinence. In men, urinary retention must not be attributable to prostate disease, and must be associated with erectile dysfunction
6. Recurrent (>1/y) falls because of impaired balance within 3 y of onset
7. Disproportionate anterocollis (dystonic) or contractures of hand or feet within the first 10 y
8. Absence of any of the common non-motor features of disease despite 5 y disease duration. These include sleep dysfunction (sleep-maintenance insomnia, excessive daytime somnolence, symptoms of REM sleep behaviour disorder), autonomic dysfunction (constipation, daytime urinary urgency, symptomatic orthostasis), hyposmia, or psychiatric dysfunction (depression, anxiety, or hallucinations)
9. Otherwise-unexplained pyramidal tract signs, defined as pyramidal weakness or clear pathologic hyperreflexia (excluding mild reflex asymmetry and isolated extensor plantar response)
10. Bilateral symmetric parkinsonism. The patient or caregiver reports bilateral symptom onset with no side predominance, **and** no side predominance is observed on objective examination

**Criteria Application:**

1. Does the patient have parkinsonism, as defined by the MDS criteria? If no, *neither* probable PD nor clinically established PD can be diagnosed. *If yes*:
2. Are any absolute exclusion criteria present? If "yes," *neither* probable PD nor clinically established PD can be diagnosed. *If no*:
3. Number of red flags present ____
4. Number of supportive criteria present ____
5. Are there at least 2 supportive criteria *and* no red flags? If yes, patient meets criteria for **clinically established PD**. *If no*:
6. Are there more than 2 red flags? If "yes," probable PD *cannot* be diagnosed. *If no*:
   Is the number of red flags equal to, or less than, the number of supportive criteria? If yes, patient meets criteria for **probable PD**

The hallmark of neuropathology in PD includes the degeneration of dopaminergic neurons in the substantia nigra pars compacta (SNpc) of the midbrain and the presence of abnormal aggregates of the α-synuclein protein, the so-called Lewy bodies.[12]

Unfortunately, the earlier mentioned diagnostic criteria only provide clinicians with a clinical diagnosis of PD and full diagnostic certainty is impossible during life. According to autopsy studies, between 75 and 95% of the patients with PD is correctly clinically diagnosed by experts.[13,14] Incorrect clinical diagnoses are mainly due to the fact that symptoms of PD can overlap with other pathologies causing parkinsonism such as multiple system atrophy, progressive supranuclear palsy, corticobasal degeneration and so forth.[15] The diagnostic accuracy is generally lower on the first visit and higher after disease progression.[16]

The clinical presentation of PD usually starts asymmetric and is dominated by the aforementioned motor symptoms such as bradykinesia, rigidity, resting tremor and postural instability. As these symptoms progress, patients generally require dopaminergic treatment that provides symptomatic relief from these motor symptoms.[17] However, these treatments do not slow down the progression of disease. As the underlying disease advances, complications related to the long-term use of those therapies emerge, including on-off fluctuations, dyskinesias and psychosis.[18-20] These complications form a substantial challenge in the clinical management of PD (Table 1.2). In addition, with advancing disease, patients develop motor impairments which are unresponsive to dopaminergic treatment (impairment of mobility and balance, difficulty with speech and swallowing), and dementia.[21] Therefore, wheelchair-dependence and nursing home placement is very common at this stage.[22,23]

**Table 1.2:** Long-term complications of dopaminergic therapies for Parkinson's disease[1]

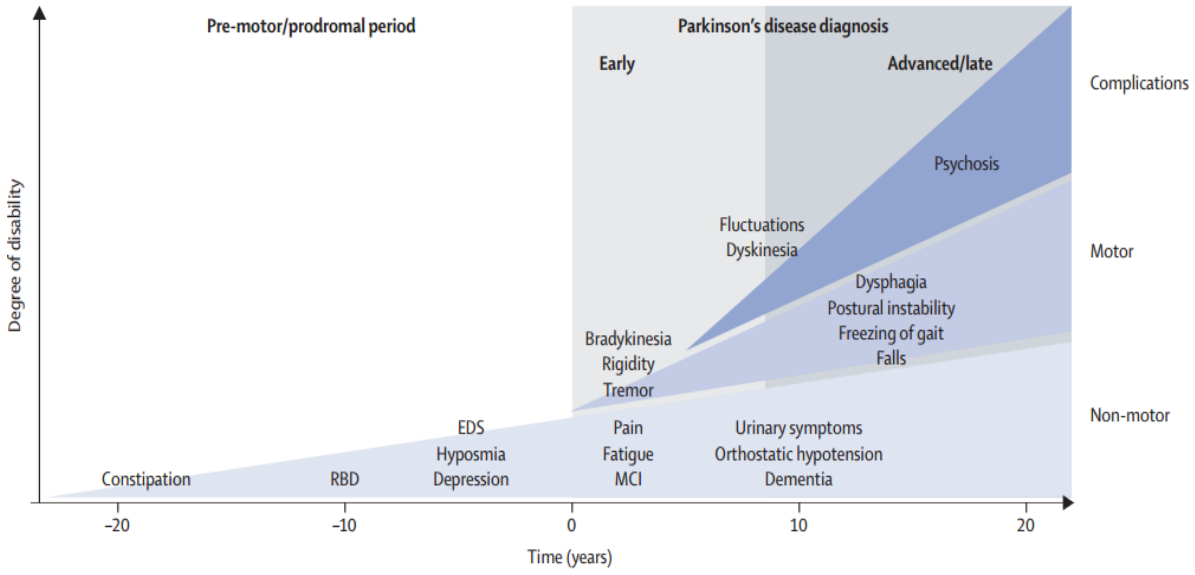
| Symptom | Definition |
|---|---|
| Motor fluctuations | Alterations between periods of good motor symptom control (i.e., on-time) and periods of reduced motor symptom control (i.e., off -time) |
| Non-motor fluctuations | Alterations between good non-motor symptom control and periods of reduced non-motor symptom control |
| Dyskinesia | Involuntary choreatiform or dystonic movements, which occur most frequently when levodopa concentrations are at their maximum (i.e., peak-dose dyskinesia); less commonly, these involuntary movements might develop at the beginning or the end of a levodopa dose, or both (i.e., diphasic dyskinesia) |
| Drug-induced psychosis | Hallucinations include minor phenomena, such as sense of presence or passage hallucinations (i.e., patients report the sensation of someone nearby or of passing in their peripheral visual field, respectively, when no one is actually there); hallucinations also include well-formed visual hallucinations, and less commonly non-visual hallucinations (e.g., auditory, tactile, olfactory); other psychotic features might include illusions and delusions (often with paranoia) |

**Non-motor symptoms**

The occurrence of non-motor symptoms in PD patients was already recognised by James Parkinson in the 19th century and several well-known non-motor symptoms such as constipation, sialorrhea, delirium and insomnia were described in his essay.[24]

It is now increasingly recognised that non-motor symptoms may predominate in the clinical presentation and substantially contribute to the disease burden and loss of quality of life (Figure 1.1, Table 1.3).[25,26] Several non-motor symptoms may even be present before the clinical diagnosis of PD.[27,28] Examples include impaired olfaction, constipation, depression, excessive daytime sleepiness (EDS) and REM-sleep behavioural disorder (RBD).[29-33] The latency period for some non-motor symptoms and the onset of clinical disease differs; for example, the average latency between onset of RBD and occurrence of parkinsonian motor symptoms is 12–14 years,[32] while the latency period for constipation can even be up to 20 years.[30]

**Figure 1.1**: Clinical symptoms and time course of Parkinson's disease progression[1]




Diagnosis of Parkinson's disease occurs with the onset of motor symptoms (time 0 years) but can be preceded by a premotor or prodromal phase of 20 years or more. This prodromal phase is characterised by specific non-motor symptoms. Additional non-motor features develop following diagnosis and with disease progression, causing clinically significant disability. Axial motor symptoms, such as postural instability with frequent falls and freezing of gait, tend to occur in advanced disease. Long-term complications of dopaminergic therapy, including fluctuations, dyskinesia, and psychosis, also contribute to disability. EDS=excessive daytime sleepiness. MCI=mild cognitive impairment. RBD=REM sleep behaviour disorder.

**Table 1.3:** The non-motor symptom complex of Parkinson's disease[34]

**Neuropsychiatric symptoms**

- Depression, apathy, anxiety
- Anhedonia
- Attention deficit
- Hallucinations, illusion, delusions
- Dementia
- Obsessional behaviour (usually drug induced), repetitive behaviour
- Confusion
- Delirium (could be drug induced)
- Panic attacks

**Sleep disorders**

- Restless legs and periodic limb movements
- Rapid eye movement (REM) sleep behaviour disorder and REM loss of atonia
- Non-REM-sleep related movement disorders
- Excessive daytime somnolence
- Vivid dreaming
- Insomnia
- Sleep disordered breathing

**Autonomic symptoms**

- Bladder disturbances
- Urgency
- Nocturia
- Frequency
- Sweating
- Orthostatic hypotension
- Falls related to orthostatic hypotension
- Coat-hanger pain
- Sexual dysfunction
- Hypersexuality (likely to be drug induced)
- Erectile impotence
- Dry eyes (xerostomia)

**Gastrointestinal symptoms (overlaps with autonomic symptoms)**

- Dribbling of saliva
- Ageusia
- Dysphagia and choking
- Reflux, vomiting
- Nausea
- Constipation
- Unsatisfactory voiding of bowel
- Faecal incontinence

**Sensory symptoms**

- Pain
- Paraesthesia
- Olfactory disturbance

**Other symptoms**

- Fatigue
- Diplopia
- Blurred vision
- Seborrhoea
- Weight loss
- Weight gain (possibly drug induced)

Non-motor symptoms in PD can present in different organ systems and the underlying pathophysiology and progression pattern for non-motor symptoms are still poorly understood; while certain non-motor symptoms (EDS, hallucinations and impulse control disorders) are believed to be caused by antiparkinsonian drugs, others are considered to be a part of the underlying disease (dementia, insomnia and autonomic dysfunction).[34] Notably, certain neuropsychiatric symptoms such as anxiety, apathy and depression could mimic other intrinsic PD symptoms.[35-38] Therefore, the diagnosis of these symptoms remains difficult in clinical practice. Concerning the general importance and the impact of non-motor symptoms on the quality of life of PD patients, knowledge on risk factors of these symptoms may help to identify patients who are at increased risk to develop these symptoms and potentially allows to postpone or even prevent their occurrence by initiating targeted interventions. To gain more insight into the course of these non-motor symptoms and to predict which patients are at risk to develop them over the course of the disease, large longitudinal studies are necessary.[39]

**Challenges in the search for predictors of non-motor symptoms**

Most studies on (the subject of the) identification of predictors for non-motor symptoms in PD have applied a cross-sectional design.[40-42] In cross-sectional studies, the exposure (risk factors) and the event (occurrence of a certain non-motor symptom) are examined at the same time point. A major drawback of this design is that it obscures the time relation between a certain variable and the occurrence of the specified event, thus no conclusions can be drawn regarding causality.[43] In longitudinal studies, the exposure and event are examined at different time points, which facilitates the detection of potential causal relationships. Longitudinal data require different analytic methods and several methods are now available, of which two will be discussed below.[44,45]

Another major requirement to identify predictors is the sample size of the study population. To determine potential associations between certain characteristics and any outcome of interest, a sufficient number of patients must develop the symptom of interest. Larger sample size are therefore required for studies on symptoms with low incidence rates.[46]

Finally, research groups that performed longitudinal studies on this subject differed concerning applied assessment methods (e.g. objective vs subjective outcome measures, diagnostic criteria vs cut-off scoring system) which could have led to an under- or overestimation of the occurrence of a certain symptom. In addition, design (e.g. clinical trials vs observational study) and target populations (e.g., population- vs hospital-based, de novo vs advanced PD) differed among studies in which the analyses were performed.[47-49] These differences may explain why studies on predictors of non-motor symptoms often yielded inconsistent results.

**Survival analysis**

In many areas of medicine, the primary interest is to find which prognostic variables may influence the time until an event occurs, such as a complication of disease or death. To determine which factors or variables shorten or prolong this period of time, one must apply a prospective study design in which a large group of patients is followed for a substantial amount of time. Both the length of follow-up and the sample size are important, because a sufficient number of patients must have developed the event of interest to obtain a solid notion of the robustness of the identified risk factors.[43-46] In survival analysis, one is interested in which factors are associated with an increased risk of a future event in patients who are free of this condition at baseline.'

In this analysis, information from patients who developed an event (uncensored) and those who did not (censored during their follow-up period) are combined. Censoring occurs if the expected event, e.g. death or onset of dyskinesias, does not occur during the follow-up period. This means that the only information available on these patients is that no event has (yet) occurred since the observation period started. In addition, censoring also occurs when an individual is lost-to-follow-up; this happens, for example, when they no longer wish to take part in study or die.

From the survival data, one can estimate the survival and death rates by using a Kaplan-Meier curve.[44] Survival rates indicate the number of patients in whom no event has occurred to a certain point in time and death rates indicate the number of patients in whom an event has occurred at a certain point in time.

To determine the simultaneous (and independent) effects of several different variables measured at baseline on the survival time, a multivariate Cox's proportional hazards model can be used.[50] The magnitude of the effect with which a certain variable influences the probability of developing a certain outcome over time, is measured as a hazard ratio (HR).[44] A hazard is the instantaneous death (or event) rate for a certain group of patients and the hazard ratio is the quotient of the hazards of two groups and indicates how much higher the event rate of one group is compared to the other. In this way, one can determine which variables increase (HR>1) or decrease (HR<1) the risk of developing a certain event.

The interpretation of the hazard ratio is based on the assumption that it remains constant over time (it is therefore also known as proportional hazards regression). This assumption is met if the risk of an event (the hazard) of group 2 is proportional to that of group 1 over the period of follow-up (constant relative hazard). Although the risk of an event (hazard) may vary over time, the variations over time must be the same in both groups.[51]

As earlier mentioned, survival analysis is one method that is applied in medical research for analysing longitudinal data. An important strength of this method is that it is very useful from a clinical perspective, especially when one is interested in predictors for dichotomous

outcomes (death/alive, dementia/no dementia). However, there are certain disadvantages to this approach. A drawback of this method is that patients with a certain symptom at baseline are excluded from follow-up and potential valuable data is lost. Another prerequisite for this method is that the outcome that one is interested in must be a dichotomous variable (yes/no, present/absent). Since many non-motor symptoms are measured as a continuous variable on a rating scale, dichotomization of these variables results in the loss of valuable information regarding these outcomes.

**Linear Mixed Models**

Linear mixed models (LMM) is another method to analyse longitudinal data that has been applied in several studies in PD.[47,52,53] This method allows for the identification of baseline variables that are associated with variation in (outcome) scores over time and provides the answer to the question “Which factors are associated with longitudinal changes in the severity of a certain symptom?” LMM takes into account that repeated measures in the same subject are not independent but correlated. A major advantage is that data from all patients are used and that this method can be applied to continuous outcomes. In addition, LMM can deal with missing data in the outcome, and therefore this analysis does not have to be restricted to patients with a complete follow-up. A similar method that allows for identification of baseline variables that are associated with variation in dichotomous/ordinal outcomes over time is the Generalized Estimating Equations (GEE) method.[54]

**Aims of the study**

The aim of this thesis is to provide information on disease progression in patients with PD, by applying longitudinal analyses to the data of the PROPARK cohort. An earlier phase of this project (called the SCOPA project, short for SCales for Outcomes in PArkinson's disease) was aimed at developing a series of clinimetric instruments for the assessment of different motor and non-motor aspects of the disease.[55-59] These instruments were applied in the PROPARK cohort (short for PROfiling PARKinson's disease), a longitudinal cohort of 421 PD patients that has been followed up for a period of 5 years (Figure 1.2). The cross-sectional analysis of the baseline data of this population has been extensively described by former researchers of our study group.[60-63] The prospective design, broad clinical characterization, the limited loss to follow-up and the size of the PROPARK cohort render this cohort very suitable for identifying predictors and factors that are longitudinally associated with different symptoms in PD.

The main objective of this thesis is to determine which factors are predictors and associated factors for the development of certain non-motor symptoms in PD, given the important role of non-motor symptoms in the disease burden and loss of quality of life.[25,26] In addition, non-motor symptoms could provide important clues to the underlying pathophysiology of PD.[34]

In **chapter 2**, we aimed to gain more insight in the risk factors of hallucinations in PD. Hallucinations in PD are often of visual nature and are considered as an important predictor for nursing home placement and mortality.[22,42] Earlier studies were somewhat inconsistent on which risk factors could predict future development of hallucinations.[48,60-64] In addition, hallucinations have long been considered a side effect of long-term levodopa treatment;[42,64] more recent studies, however, have questioned this assumption, as a relation with levodopa dosage has not been consistently found.[48,63] Our study could contribute to this knowledge by identifying new predictors and confirming (or refuting) those that have been found in the past. This information may facilitate the identification of patients at risk and the adequate management of those patients.

In **chapter 3,** we examined the main predictors of dementia in PD. Compared to subjects in the general population, PD patients have a six-times higher risk to develop dementia.[65] Moreover, according to an Australian prospective study of 136 PD patients, 80% of the remaining 20-year survivors eventually developed dementia.[66] This emphasizes the importance of large longitudinal cohorts and identifying risk factors for this debilitating symptom. Our cohort is ideal for this purpose because of its large sample size and long follow-up duration.

In **chapter 4,** we aimed to further our understanding of the causes of excessive daytime sleepiness (EDS) in PD. This symptom has mainly come to attention after an earlier case report that studied 8 PD patients who were involved in automobile accidents due to a sudden onset of sleep, while being treated with dopamine agonists.[67] Most previous studies on this topic in PD had a cross-sectional design and to date only two longitudinal studies have been performed, which both suggest a strong association between dopamine agonist use and EDS.[47,68] In our analysis, we wanted to verify whether the development of EDS symptoms over time was indeed associated with the use of dopamine agonists, and if other risk factors may play a role.

PD patients often experience problems with sleep during the night. Night-time sleep disorders in PD can present in different forms and often have a multifactorial origin (Table 1.4).[69,70] Insomnia is common in PD and is defined as problems involving initiating sleep, maintaining sleep, early awakenings and a poor overall sleep quality.[71] In PD, sleep fragmentation and early awakenings are the most common complaints, whereas initiation of sleep is often unimpaired.[69] To date only one large longitudinal study (n=231) has been performed on this topic,[53] which showed that insomnia often exhibits a fluctuating course and is associated with female gender, longer disease duration and coexistent depression. More knowledge of risk factors for insomnia may provide clues for an enhanced understanding of the underlying pathophysiology, facilitate early detection and guide future intervention strategies. Therefore, we examined the course and factors associated with longitudinal changes in the severity of insomnia in PD in **chapter 5**.

**Table 1.4:** Sleep Disturbances in Parkinson's Disease[70]

**Due to nocturnal recurrence of PD symptoms**
- Tremor
- Difficulty turning over in bed
- Rigidity
- Painful cramps

**Due to conditions that are associated with PD**
- Depression
- Anxiety
- Restless legs syndrome
- Periodic limb movement disorder
- Rapid eye movement (REM) behaviour disorder
- Dementia
- Sleep apnoea
- Nocturnal urination
- Excessive daytime napping

**Due to medications used to treat PD**
- Dopamine agonist induced insomnia
- Side effects of selegiline, anticholinergics, amantadine
- Vivid dreams, nightmares
- Hallucinations

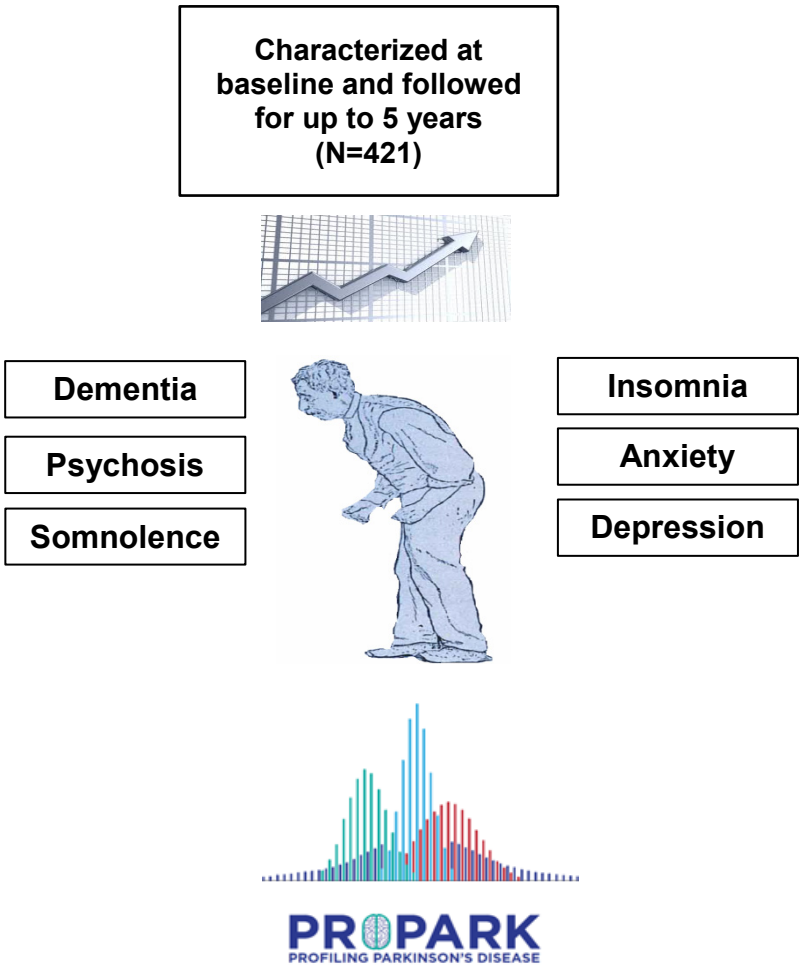
**Due to other conditions**
- Medical conditions
    - Arthritis
    - Cardiac or pulmonary disorders
    - Reflux
    - Infections
    - Prostate hypertrophy
    - Pain not due to PD
- Medication used to treat medical conditions
- Withdrawal from sedative/hypnotics
- Emotional conditions
    - Stress
    - Anxiety
    - Reactions to major life events

In **Chapter 6 and 7** two neuropsychiatric symptoms that are common in PD are addressed: anxiety and depression. Depression is an important determinant of poor quality of life in PD patients.[72] Identification of depression in PD is especially difficult since there is a significant overlap with symptoms primarily related to PD or those related to side effects of the use of medication.[73] Past longitudinal studies found that female gender, longer disease duration, greater disability and long-term levodopa use are associated with the development of depression in PD.[74-76] However, due to the fact that the number of baseline features used in these analyses were limited, not much is known on the relationship between other symptoms and depression. This is especially true for many non-motor symptoms, which is unfortunate since these features often have a non-dopaminergic origin and are therefore less sensitive to dopaminergic medication; including these symptoms in the analysis therefore provides a more complete and more accurate evaluation of disease severity and progression in PD.[77] In

**chapter 6**, we aimed to provide a more thorough picture of the course of depression in our cohort, and examined its risk factors.

Anxiety is frequently under-recognized in PD and studies in the past have mainly focused on depression, even though some studies suggest that anxiety may contribute more importantly to morbidity in PD.[78,79] Longitudinal studies performed in the general population found that female gender, comorbidity, and psychological factors such as the number of stressful events or certain personality traits could play a role in the development of anxiety.[80,81] In PD, only one longitudinal study has been performed in 89 mildly affected PD patients, who were followed over a relatively short period of 1.5 years.[82] This means that information on the course of anxiety in PD as well as on the factors associated with longitudinal changes in this feature are very limited. Given the size and length of follow up of our cohort, an analysis of the data pertaining to this topic may contribute importantly to the knowledge in this field and this is described in **chapter 7**.

**Figure 1.2** SCOPA-PROPARK cohort



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Chapter 2:

# Risk Factors for Hallucinations in Parkinson's Disease: Results From a Large Prospective Cohort Study


Kangdi Zhu[1]; Jacobus J. van Hilten[1];Hein Putter[2]; Johan Marinus[1]

[1]Department of Neurology, Leiden University Medical Center, Leiden, The Netherlands
[2]Department of Medical Statistics and BioInformatics, Leiden University Medical Center, Leiden, The Netherlands

Published in *Movement Disorders* 2013;28:755-762

**ABSTRACT**

The aim of this study was to identify risk factors for the development of hallucinations in patients with Parkinson's disease (PD). A broad range of motor and nonmotor features was assessed at baseline and during the following 5 years in 386 PD patients. Cross-sectional analyses of baseline data and longitudinal analyses of follow-up data were performed to identify risk factors for hallucinations in PD. Twenty-one percent of the patients had hallucinations at baseline, whereas 46% of the patients without hallucinations at baseline developed this feature during follow-up. Univariate survival analysis showed that older age, female sex, less education, higher age at onset, and more severe motor and cognitive impairment, depression, daytimes sleepiness, autonomic dysfunction, and motor fluctuations and dyskinesias, as well as higher daily levodopa dose, were associated with the risk of developing hallucinations. This largely corresponds with the features that were associated with the presence of hallucinations at baseline. In a stepwise regression model, older age at onset, female sex, excessive daytime sleepiness, autonomic dysfunction, and dyskinesias emerged as independent risk factors for developing hallucinations. Female sex, autonomic dysfunction, motor fluctuations, and dyskinesias have not been reported as risk factors in previous studies. These findings lend support to the notion that hallucinations in PD are caused by a combination of risk factors that are associated with (the interaction between) older age and more advanced disease. The identification of female sex as a risk factor for developing of hallucinations in PD is a new finding and should be verified in future studies.

## INTRODUCTION

Parkinson's disease (PD) is a progressive multisystem disorder that is associated with an increased risk of developing psychotic symptoms such as illusions and hallucinations. In PD, hallucinations may manifest in a variety of forms, with visual hallucinations the most prevalent.[1,2] Hallucinations can be benign with retained insight, but can also occur without insight and perceived as threatening.[1] The prevalence of hallucinations in PD may vary from 33% to 63%, with probability and severity increasing over the course of disease.[3] They are associated with abnormal behavior and increased probability of nursing home placement and mortality.[4,5] In view of these severe consequences, early identification of patients at risk of developing hallucinations is important, and thorough knowledge of potential factors that may predict future development of hallucinations is therefore indispensable and a prerequisite for adequate management. Previous studies identified various risk factors for developing hallucinations in PD, such as older age, older age at onset, longer disease duration, depression, sleep disturbances (insomnia, REM-sleep behavioural disorder [RBD], and excessive daytime sleepiness), cognitive impairment, severity of motor symptoms, and comorbidity.[1,3,6–14] Hallucinations have also long been considered a side effect of long-term levodopa treatment[2]; more recent studies, however, have questioned this assumption, as a relation with levodopa dosage level has not been consistently found.[3,13–17]

Previous studies on hallucinations in PD have often yielded inconsistent results. This may evidently be a result of differences in population characteristics and methodological issues. The latter include small sample size[6,7,9] and low prevalence of patients with hallucinations.[3,18] Another important aspect is the design of the study; most studies used a cross-sectional design, which obscures the time relation between potential risk factors and emergence of hallucinations. Longitudinal studies are therefore preferred. Unfortunately, large longitudinal studies with several years of follow-up are scarce in PD. The length of follow-up is important, though, because a sufficient number of patients must have developed hallucinations to obtain a solid notion of the robustness of the identified risk factors.

We found 3 prospective studies dealing with predictors of hallucinations in PD that followed more than 100 patients, with follow-up periods of 1, 4, and 12 years.[3,18,19] However, these studies only analysed a limited number of potential risk factors. For the purpose of the present study, data from the PROPARK cohort were used. This is a longitudinal study of more than 400 PD patients who are broadly characterized and have been examined annually and followed up for 5 years (i.e. 6 assessments).[20] These characteristics make this study very well suited for the purpose of identifying risk factors for the development of hallucinations in patients with PD. Analyses include a cross-sectional examination of baseline data as well as a longitudinal analysis of follow-up data.

## PATIENTS AND METHODS

*Study Design and Participants*

Patients were recruited from neurology clinics of university and regional hospitals in the western part of the Netherlands, and all fulfilled the United Kingdom Parkinson's disease Society Brain Bank criteria for idiopathic PD.[21] Given that we intended to obtain information on the full spectrum of the disease, a recruitment strategy based on age at onset (≤50 years or >50 years) and disease duration (≤10 years or >10 years) was applied. We aimed to recruit at least 100 patients in each of the 4 strata. The majority of the patients were evaluated at the Leiden University Medical Center, but more severely affected patients were offered the possibility to be examined at their homes to prevent selective dropout as much as possible. More detail on the design of the PROPARK study can be found elsewhere.[20] The medical ethical committee of the Leiden University Medical Center approved the PROPARK study, and written informed consent was obtained from all patients.

*Assessment of Hallucinations*

Patients were considered to have hallucinations if a score≥1 was obtained on the hallucinations item of the SCOPA-Psychiatric Complications scale (SCOPA-PC).[22]
In the SCOPA-PC a semistructured interview is used to elicit information. The hallucination item of this instrument covers visual, auditory, tactile, and olfactory hallucinations. The items address the occurrence of these events in the past month and are rated as 0=absent, 1=mild, 2=moderate, or 3=severe. Mild hallucinations (score of 1) involved hallucinations with insight, whereas moderate hallucinations (score of 2) concerned hallucinations with partial insight for which patients could be convinced that their hallucinations were not real. Patients with severe hallucinations (score of 3) had no insight, and the hallucinations were often perceived as threatening.[22] In addition, patients were also considered to suffer from hallucinations if they used quetiapine or clozapine, because both drugs are specifically prescribed for hallucinations[23]; because rivastigmine is prescribed for both cognitive problems and hallucinations,[24,25] only patients who, according to the patients' records, received this drug because of hallucinations were counted as hallucinators.

*Assessment of Baseline Variables*

At baseline (2003–2005) and at the 5 following annual visits, all patients received standardized assessments. The assessments included an evaluation of demographic and clinical characteristics, family history of PD, and the use of antiparkinsonian medication. For each patient, a levodopa equivalent (LDE) of levodopa and dopamine agonist dose was calculated at baseline. Total LDE is the sum of levodopa dosage equivalent (LDE-dopa) and dopamine agonist dosage equivalent (LDE-

DA).[26] Hoehn & Yahr (H&Y) stages of the patients were ascertained at every assessment.[27] Measurement instruments for the different clinical domains of PD were derived from the SCOPA project and have all been found valid and reliable. The following instruments were administered by a qualified examiner: the SPES/SCOPA (including sections on motor examination, activities of daily living, and motor complications),[28] the SCOPA-COG (cognitive function),[20] and the SCOPA-PC.[22] Patients completed the following instruments: the SCOPA-AUT(autonomic complaints),[29] the SCOPA-SLEEP (with sections on nighttime sleep problems and daytime sleepiness),[30] and the Beck Depression Inventory.[31] For all instruments except the SCOPA-COG, higher scores reflect poorer functioning.

*Clinical Subtypes of PD*

Recently, van Rooden et al identified 4 clinical subtypes of PD using a data-driven approach.[32] The numbers of patients with subtypes 1, 2, 3, and 4 were 169, 45, 101, and 26, respectively, and subtype data were missing for 45 patients who were included at baseline. With increasing subtype number, patients are clinically characterized by more severe symptoms of the nondopaminergic domains especially. In addition, patients with subtypes 2 and 4 have more severe motor complications than those with subtypes 1 and 3, whereas patients with subtypes 1 and 2 are younger and have a younger age at onset than those with subtypes 3 and 4. For more detail, see the publication by van Rooden et al.[32]

*Inclusion and Exclusion Criteria*

Patients who underwent deep brain stimulation (DBS) before the start of the study were excluded from the cross-sectional baseline analysis; patients who underwent DBS during follow-up contributed time up to the last annual assessment before DBS. Only patients who had no hallucinations at baseline were included in the longitudinal analysis. In addition, patients who were only assessed in year 1 and did not show up for later annual assessments were excluded from the longitudinal analysis.

*Statistical Analysis*

Cross-sectional analyses to assess differences at baseline between PD patients with and without hallucinations were performed as appropriate. In the longitudinal analyses we first performed univariate analyses to evaluate which baseline variables were associated with the later development of hallucinations. The following baseline variables were taken from the literature and were included if they had been shown to contribute significantly to the

development of hallucinations in 1 or more studies: age, age at onset of PD, disease duration, Hoehn & Yahr stage, cognitive function, comorbidity, excessive daytime sleepiness, depression, hypokinesia, rigidity, postural instability and gait disorder, and the use of antiparkinsonian medication.[1,3,6–14] Furthermore, a few other baseline variables were added because a relation with development of hallucinations could be presumed: sex, education, tremor, motor fluctuations, number of falls in the past year, dyskinesias, autonomic dysfunction, and nighttime sleep problems. Education is closely related to cognitive disorders and may therefore be considered a risk factor. Motor fluctuations and dyskinesias are associated with the use of antiparkinsonian medication, which in turn are related to the development of hallucinations. Autonomic symptoms and falling are related to comorbidity, but may also serve as indicators of disease severity. All baseline variables with a $P<.10$ in the univariate analysis were subsequently included in the multivariate Cox proportional hazards model with a backward-selection approach. In addition, in a separate Cox regression analysis, the differences in the probability of developing hallucinations among the 4 clinical subtypes were examined while the influence of confounders was taken into account. Kaplan–Meier curves (i.e., unadjusted) were also used to illustrate the differences in survival times. The associations between baseline variables and the development of hallucinations were calculated as hazard ratios (HRs) with 95% confidence intervals (CIs). An $HR>1$ indicates that the variable is associated with a higher risk of developing hallucinations during follow-up. $P<.05$ was considered significant.

*Calculation of Survival Time*

Follow-up ended at the date of the final follow-up visit (for those still without hallucinations), the date of the last examination before loss to follow-up, or the date of the examination at which hallucinations were observed, whichever came first. Survival time was calculated as the difference between these dates and the date of the patient's baseline assessment. Patients were considered to have an event ("uncensored") if they scored≥1 on the hallucinations item of the SCOPA-PC or if they used quetiapine, clozapine, or rivastigmine for hallucinations. If a patient did not have an event during the complete follow-up, he or she was withdrawn alive and classified as "censored." In addition, if a patient underwent DBS or died during follow-up, survival time was calculated as the difference between the date of the last assessment before DBS or death and the date of the baseline assessment. If a patient had missed 1 year and had no hallucinations in the previous and following years, we assumed that the patient did not have hallucinations in that particular year. All analyses were performed with Statistical Package for the Social Sciences (SPSS) version 18.0.

## RESULTS

*Hallucinations*

A total of 386 patients were included at baseline, of whom 81 (21.0%) had hallucinations and/or used medication for hallucinations (Figure 2.1, Table 2.1). Twenty-five of these patients also suffered from paranoid ideation. Patients without hallucinations at baseline (n=305) were followed for a maximum of 5 years; of these, 28 patients (9.2%) were lost to follow-up during the first year because they died (n=5), lost interest in the study (n=13), or considered the study too demanding (n=10). Thus, a total of 277 patients remained for inclusion in the longitudinal analysis. Patients with hallucinations at baseline were older, had longer disease duration, and had higher H&Y scores (Table 2.1). In addition, patients with hallucinations had more severe cognitive impairment, depression, daytime sleepiness, and dyskinesias. Patients with hallucinations also had more postural instability and gait disorder (PIGD), fell more often, and used higher daily doses of levodopa and dopamine agonists. The 28 patients who stopped after the baseline assessment were older (65.4±14.3 vs 59.4±11.0 years, P=.048) and were more severely affected by the disease as measured by H&Y (median, 3.00 vs 2.00;U=4508; z=2.029; P=.042). Patients without hallucinations at baseline (n=277) were followed up for a maximum of 5 years, and 126 of them (45%) developed hallucinations. Univariate analyses showed that older age at examination, older age at onset, female sex, and fewer years of education were associated with an increased risk of hallucinations (Table 2.2). Of the motor symptoms, PIGD, dyskinesias, and motor fluctuations predicted future onset of hallucinations. Other baseline characteristics that were associated with an increased probability of developing hallucinations were higher H&Y score, lower cognition, more severe daytime sleepiness, autonomic dysfunction, and depression, as well as higher daily levodopa dose. All baseline variables that showed univariate associations (P<.10) with hallucinations were entered in the multivariate analysis, after which older age at onset, female sex, excessive daytime sleepiness, autonomic dysfunction, and dyskinesias emerged as independent risk factors in the Cox proportional hazards regression analysis (Table 2.3).

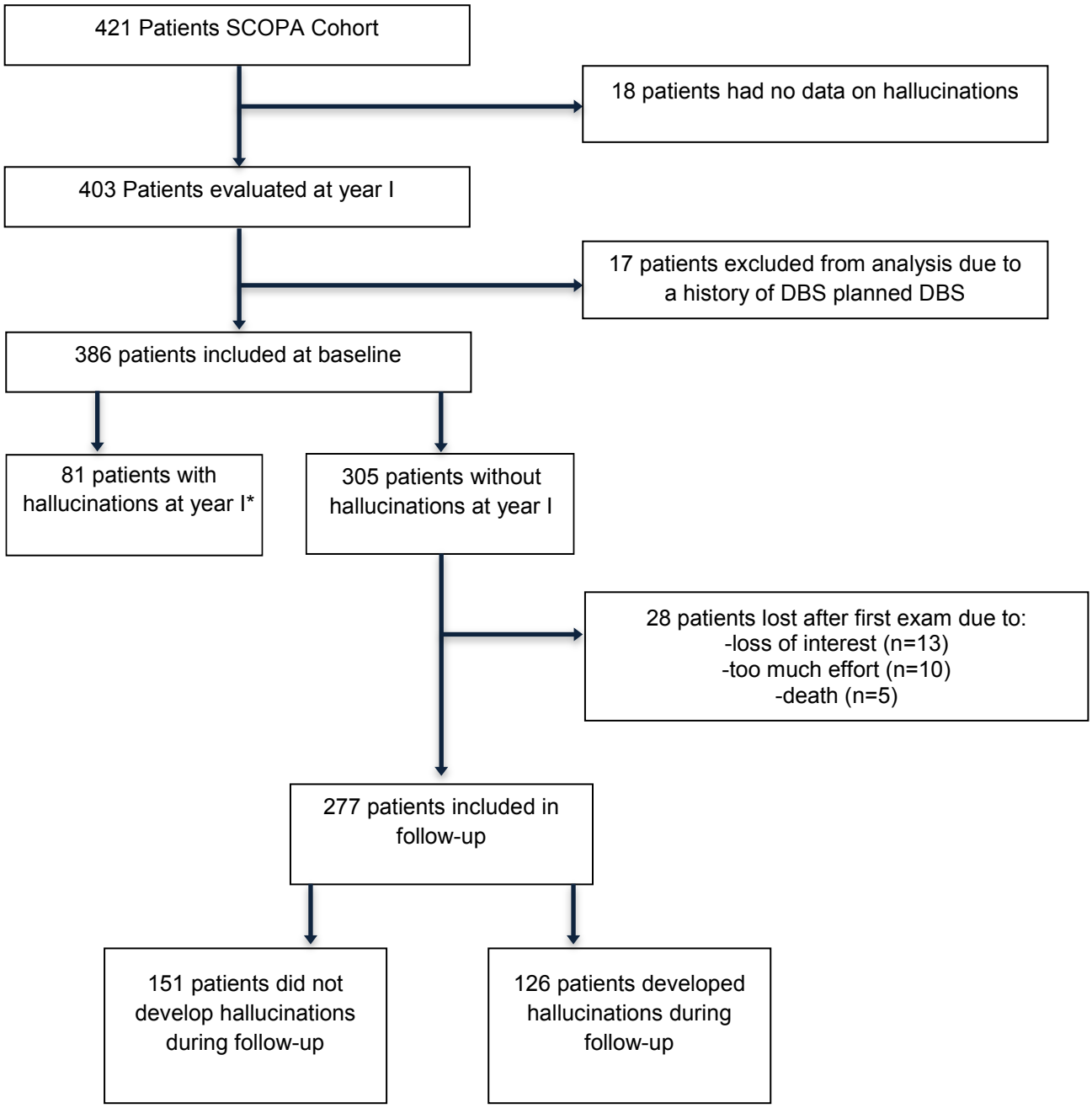
**Table 2.1:** Baseline data of patients with and without hallucinations

| | Total | With hallucinations | Without hallucinations | p-values |
|---|---|---|---|---|
| N | 386 | 81 | 305 | |
| Age, y | 61.06 (11.46) | 65.38 (10.62) | 59.91 (11.41) | <0.001 |
| Sex, % male | 63.5 | 59.3 | 64.6 | 0.376[a] |
| Education, y | 11.98 (4.11) | 11.34 (4.43) | 12.14 (4.01) | 0.118 |
| Age at onset, y | 50.93 (11.82) | 52.32 (10.96) | 50.56 (12.03) | 0.232 |
| Disease duration, y | 10.13 (6.19) | 13.05 (6.15) | 9.36 (5.97) | <0.001 |
| Hoehn & Yahr, stage | 2 (2,3) | 3 (2,4) | 2 (2,3) | 0.001[b] |
| Tremor score | 3.71 (2.04) | 3.49 (2.28) | 3.77 (1.98) | 0.296 |
| Bradykinesia/rigidity score | 5.06 (2.02) | 5.36 (2.26) | 4.99 (1.96) | 0.157 |
| PIGD | 2.3 (1.92) | 3.04 (2.21) | 2.11 (1.79) | 0.001 |
| Dyskinesia score | 0.86 (1.57) | 1.51 (1.81) | 0.7 (1.45) | <0.001 |
| Motor Fluctuations | 0.73 (1.23) | 0.97 (1.34) | 0.67 (1.19) | 0.070 |
| Number of falls past year | 0 (0-2) | 1 (0-5) | 0 (0-1) | <0.001[b] |
| SCOPA-COG | 25.55 (6.67) | 20.9 (7.83) | 26.79 (5.74) | <0.001 |
| Beck Depression Inventory | 10.09 (6.55) | 13.3 (7.29) | 9.25 (6.08) | <0.001 |
| SCOPA-SLEEP - nighttime | 4.45 (3.75) | 5.18 (3.84) | 4.25 (3.71) | 0.051 |
| SCOPA-SLEEP - EDS | 4.88 (3.73) | 6.73 (4.14) | 4.39 (3.46) | <0.001 |
| SCOPA-AUT, total score | 10.44 (5.67) | 13.03 (5.95) | 9.78 (5.41) | <0.001 |
| Total LDE | 577 (437) | 771 (452) | 525 (419) | <0.001 |
| Daily levodopa dose, mg | 349 (365) | 493 (370) | 311 (331) | <0.001 |
| Daily DA dose, mg | 227 (224) | 278 (232) | 214 (220) | 0.022 |

*Variables are expressed as means (standard deviations (SD)), except for gender (percentages), and Hoehn and Yahr stage and number of falls past year (median (interquartile range)). All differences are calculated with the independent-samples t-tests, except for [a] Chi-square test and [b] Mann-Whitney U test.*

*SCOPA-COG: cognitive function, higher scores reflect better functioning; SCOPA-SLEEP, nighttime: nighttime sleep problems; SCOPA-SLEEP, EDS: daytime sleepiness; SCOPA-AUT, total score: sumscore autonomic functioning including items from the sections on gastrointestinal, cardiovascular and urinary tract; LDE: Total levodopa dosage equivalent; DA: Dopamine agonists; PIGD: Postural instability gait disorder.*

**Figure 2.1:** Flow Chart of follow-up for hallucinations




*15 used medication, 54 had hallucinations, 12 had both

**Table 2.2:** Univariate associations between baseline characteristics and risk of hallucinations

| | Hazard Ratio (95% CI) | P-values |
|---|---|---|
| Age, y | 1.039 (1.022-1.057) | <0.001 |
| Sex, HR for females[a] | 1.656 (1.164-2.355) | 0.005 |
| Education, y | 0.953 (0.909-0.999) | 0.044 |
| Age at onset, y | 1.029 (1.012-1.045) | 0.001 |
| Disease duration, y | 1.016 (0.988-1.045) | 0.272 |
| Hoehn & Yahr stage | 1.426 (1.152-1.766) | 0.001 |
| Tremor score | 1.041(0.955-1.134) | 0.360 |
| Bradykinesia/rigidity score | 1.070(0.978-1.171) | 0.138 |
| PIGD score | 1.220(1.111-1.340) | <0.001 |
| Dyskinesia score | 1.201(1.080-1.336) | 0.001 |
| Motor Fluctuations | 1.200(1.050-1.371) | 0.008 |
| Number of falls past year | 1.004(0.998-1.006) | 0.402 |
| SCOPA-COG | 0.938(0.908-0.969) | <0.001 |
| Beck Depression Inventory | 1.045(1.021-1.070) | <0.001 |
| SCOPA-SLEEP - nighttime | 0.992(0.946-1.040) | 0.740 |
| SCOPA-SLEEP - EDS | 1.079(1.030-1.130) | 0.001 |
| SCOPA-AUT, total score | 1.103(1.069-1.138) | <0.001 |
| Total LDE | 1.000(1.000-1.001) | 0.070 |
| Daily Levodopa Dose, mg | 1.001(1.000-1.001) | 0.001 |
| Daily DA Dose, mg | 0.999(0.999-1.000) | 0.159 |

*All variables are expressed with hazard ratio (HR) with 95% confidence interval.*
*[a]Fifty-five of 97 women (56.7%) developed hallucinations during follow-up vs 71/180 (39.4%) men.*
*EDS: Excessive Daytime Sleepiness; PIGD: Postural-instability-gait disorder; LDE: Levodopa dosage equivalent; DA: Dopamine agonists.*

**Table 2.3:** Summary of Cox Proportional hazards model for hallucinations in Parkinson's Disease

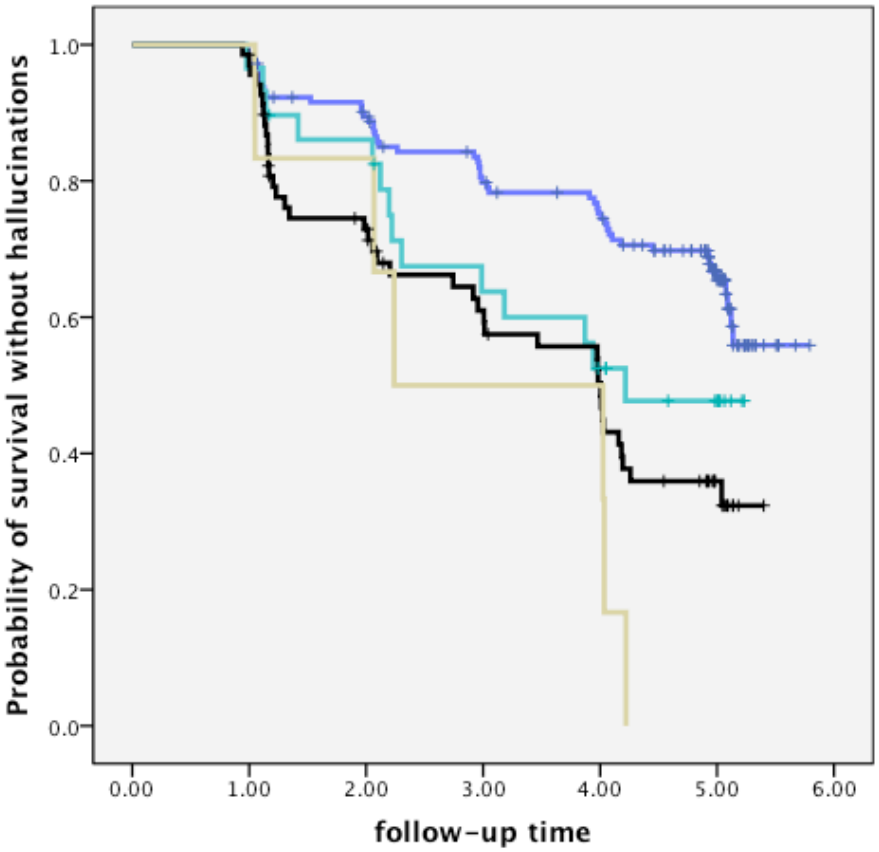
| | Hazard Ratio (95% CI) | P-values |
|---|---|---|
| Sex, HR for females | 1.619 (1.099-2.383) | 0.015 |
| Age at onset, yr | 1.030 (1.011-1.049) | 0.002 |
| Dyskinesia score | 1.164 (1.023-1.324) | 0.021 |
| SCOPA-SLEEP - EDS | 1.087 (1.030-1.147) | 0.003 |
| SCOPA-AUT, total score | 1.062 (1.019-1.106) | 0.004 |
| Age, yr | 0.985(0.941-1.031) | 0.803 |
| Education, yr | 1.008(0.955-1.063) | 0.781 |
| SCOPA-COG | 0.994(0.955-1.035) | 0.760 |
| Beck Depression Inventory | 1.005(0.969-1.041) | 0.803 |
| PIGD score | 1.024(0.870-1.204) | 0.778 |
| Hoehn & Yahr stage | 1.125(0.868-1.459) | 0.372 |
| Motor Fluctuations | 1.166(0.972-1.400) | 0.099 |
| Total LDE | 1.000(0.999-1.000) | 0.238 |
| Daily Levodopa Dose, mg | 1.001(1.000-1.002) | 0.156 |

*All variables are expressed with hazard ratio (HR) with 95% confidence interval.*
*EDS: Excessive Daytime Sleepiness; PIGD: Postural-instability-gait disorder; LDE: Levodopa dosage equivalent; DA: Dopamine agonists.*

*Influence of Clinical Subtypes*

Information on subtype classification was available for 247 of the 277 patients (89.2%) without hallucinations at baseline. Clinical subtypes could not be determined in the other patients because some values required for the correct classification were missing. In the model with adjustment for differences in age, sex, and disease duration, we found that patients with more severe disease and stronger progression (subtypes 3 and 4) had a significantly increased risk of developing hallucinations compared with those with subtype 1 (reference category). Compared with subtype 1 (HR=1), patients with subtype 2 had an HR of 1.40 (95% CI, 0.78–2.52), whereas patients with subtypes 3 and 4 had an HR of 1.80 (95% CI, 1.22–2.68) and 3.70 (95% CI, 1.60–8.57), respectively. Post hoc analyses showed no further differences in risks among subtypes 2, 3, and 4. Figure 2 shows the Kaplan–Meier curves of the 4 clinical subtypes. The log-rank test, a test that does not account for baseline differences between the subtypes, was significant at P<.001.

**Figure 2.2:** Kaplan-Meier curves displaying unadjusted risk for developing hallucinations for 4 clinical subtypes of PD.




*1. mild symptoms*

*2. motor complications*

*3. non-dopaminergic symptoms*

*4. severe symptoms*

## DISCUSSION

The cross-sectional analysis showed that approximately 20% of the patients had hallucinations at baseline, whereas the longitudinal analysis showed that almost half the patients without hallucinations at baseline developed this symptom during the 5-year follow-up period. Variables that showed significant associations in the cross-sectional analyses largely corresponded to the risk factors that emerged as significant predictors by the longitudinal analyses, with the exception of disease duration, daily dopamine agonist dose, number of falls in the past year (significant only in the cross-sectional analyses), age at onset of PD symptoms, female sex, years of education, and presence of motor fluctuations (significant only in the longitudinal analyses). Risk factors reported in earlier studies that were confirmed by our longitudinal analyses were older age at examination, older age at onset, fewer years of education, higher H&Y stage, postural problems, impaired cognition, depression, excessive daytime sleepiness, and higher dose of levodopa.[3,7,13-15,33-35] With the exception of education, these factors all reflect to some extent the intricate relation between older age and advanced disease that underlies so many late complications of PD. Risk factors identified in the longitudinal analysis that have not been reported earlier as risk factors for hallucinations are female sex, autonomic dysfunction, motor fluctuations, and dyskinesias, and these risk factors will therefore be discussed in greater detail.

That female sex emerged as a risk factor neither in previous studies nor in our analysis of baseline data evidently leaves open the possibility that we are dealing here with a chance finding. However, the numbers on which the longitudinal analysis was based are quite robust: 55 of the 97 women (57%) versus 71 of the 180 men (39%) without hallucinations at baseline developed this symptom during follow-up. Because levodopa treatment was found to be associated with increased risk of developing hallucinations, one explanation might be that female PD patients have a higher sensitivity to dopaminergic medication.[36] This is partly supported by the finding that levodopa-induced dyskinesias, which also emerged as a risk factor in the longitudinal analysis, occur earlier in female patients[37] and by the observation that they were associated with hallucination scores in our study ($r_s$=0.227, P<.001). A possible explanation for the increased sensitivity to levodopa could be the greater amount of levodopa per kilogram, but our data did not support this assumption (4.06±4.72 mg/kg for women vs 3.93±4.53 mg/kg for men, P=.823). However, this does not rule out a potential effect of higher bioavailability and lower clearance of medication in female patients, possibly mediated by estrogen.[38] A difference in Lewy body deposition or amyloid-β plaques between men and women would also explain our findings,[39] although, to our knowledge, such a difference between male and female patients with PD has not been reported. A final possibility is that disease progression in women is faster, and given that disease

severity is associated with the risk of hallucinations, this could explain the observed result. This assumption is supported by findings from the Sydney Multicenter Study,[40] in which it was observed that women progressed at a similar rate to men until 8 years, when the severity of their disease as measured by Hoehn and Yahr stage became greater. Given the relatively long disease duration in our cohort (10.1±6.2 years for the total population at baseline, 13.1±6.2 years for those with hallucinations at baseline), this possibility should be explored. When we looked at the baseline data, we indeed found that men and women had similar disease duration (9.91±7.58 years for women vs 9.95±6.59 years for men, P=.959), but that women had a significantly higher mean H&Y score (2.75±0.93 for women vs 2.44±0.76 for men, P=.005). In addition to the arguments mentioned above, it should be considered that community-based studies on the occurrence of hallucinations in the general population have shown that women are at higher risk of experiencing hallucinations at some time during their lives than are men.[41] Therefore, future studies are needed to examine the main effect of sex and the possible interaction between sex and levodopa on the risk of developing hallucinations in PD.

That autonomic dysfunction has not been reported in earlier studies may largely be because to date its role in predicting hallucinations in PD has hardly been investigated. We found only 1 study, by Biglan et al,[3] who examined the role of comorbidity in PD and found that disturbances in more than 5 organ systems was a risk factor for hallucinations. In the present study we used the items of the SCOPA-AUT that pertained to 3 organ systems: the gastrointestinal tract, the urinary tract, and the cardiovascular system. We found that not only the total score but also the 3 separate scores were independently associated with future development of hallucinations (data not shown). This relation may be explained by more severe autonomic dysfunction reflecting more advanced disease; autonomic dysfunction has been identified before as 1 of a set of variables—together with axial, psychotic, and depressive symptoms, daytime sleepiness, and cognitive impairment—that form a strong independent factor (factor 1 in the study by van Rooden et al)[42] that is associated with disease severity (as measured by H&Y) and disease duration. It is not surprising that dyskinesias and motor fluctuations emerged as risk factors for hallucinations, because these complications are well documented side effects of long-term levodopa treatment.[43] That total LDE was not identified as an independent risk factor could have been because of the close relation between levodopa treatment and dyskinesias. To examine this, we removed dyskinesias from the multivariate model, after which the contribution of total LDE was found to be significant. Hence, long-term levodopa treatment may lead to dyskinesias, and both are associated with the occurrence of hallucinations. Subtype classifications were not available for 30 of the 277 patients (10.8%) without hallucinations at baseline. No significant differences in age, sex, disease duration, and H&Y stage were found between these 30

patients and the patients who were included in the analysis, which indicates that it is unlikely that the absence of information on subtype allocation poses a threat to the validity of our findings. Patients who were mildly affected by the disease (subtype 1) were less likely to develop hallucinations at any time during follow-up compared with patients with subtypes 3 and 4. Patients who were severely affected on all domains (subtype 4) eventually all developed hallucinations at some point during follow-up, although it should be noted that this involved only 6 patients. This further supports the notion that hallucinations are a symptom of more severe disease.

A limitation of our study is that we were not able to verify the relationship between some potential risk factors and the development of hallucinations because these variables were not evaluated at baseline. For example, visual disturbances and RBD are well-documented risk factors of visual hallucinations in PD reported in earlier studies[3,6,9,18] but were not included here. That the 28 patients who dropped out of the study in the first year had older age at onset and more advanced disease may have led to an underestimation of the HRs, but this did not affect the validity of our findings. Strong points of this study are the large number of patients, the longitudinal design, the broad characterization of the patients, and the long follow-up duration.

To summarize, hallucinations in PD are caused by a combination of risk factors that are associated with (the interaction between) older age and more advanced disease. Older age, older age at onset, longer disease duration, and more advanced motor symptoms, as well as more severe depressive and autonomic symptoms, cognitive impairment, sleep disturbances and higher levodopa dose are associated with development of these symptoms. This indicates that patients with these characteristics must be examined carefully for the presence of hallucinations, and more frequent follow-up should be considered. If symptoms are present, the medication regimen should be adjusted. The identification of female sex as a risk factor for developing of hallucinations in PD is a new finding and should be verified in future studies.

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Chapter 3:

# Predictors of dementia in Parkinson's disease; findings from a 5-year prospective study using the SCOPA-COG


Kangdi Zhu[1]; Jacobus J. van Hilten[1]; Johan Marinus[1]

[1]Department of Neurology, Leiden University Medical Center, Leiden, The Netherlands

Published in *Parkinsonism and Related Disorders* 2014;20:980-985

**ABSTRACT**

*Objective.* Aim of this study was to identify risk factors for the development of dementia in patients with Parkinson's disease (PD). *Methods.* A broad range of motor and non-motor features was assessed at baseline and the following five years in 406 PD patients. Cross-sectional analyses of baseline data and longitudinal analyses of follow-up data were performed to identify risk factors for dementia. *Results.* Thirty-two percent of patients (n = 129) had dementia at baseline, while 26% of patients (n = 68) without dementia at baseline developed dementia during follow-up. Univariate survival analysis showed that higher age, fewer years of education, longer disease duration, higher age-at-onset, higher levodopa dose, higher Hoehn & Yahr stage, presence of dyskinesias, excessive daytime sleepiness (EDS), presence of hallucinations, and more severe autonomic and depressive symptoms were associated with an increased risk of dementia. Higher baseline Postural-Instability-and-Gait-Difficulty scores were also associated with an increased risk of dementia, whereas no effect of tremor severity was found. These findings largely corresponded with the variables that were associated with the presence of dementia at baseline. In a stepwise regression model, higher age at baseline, fewer years of education, higher daily levodopa dose and excessive daytime sleepiness (EDS) emerged as independent risk factors of future dementia. *Conclusions.* In this large prospective cohort study, we identified a combination of potentially interacting risk factors for dementia in PD that are associated with higher age and more advanced disease.

## INTRODUCTION

Dementia is one of the most devastating consequences of Parkinson's disease (PD). While the prevalence of dementia is estimated at 30% in cross-sectional studies,[1] findings from longitudinal studies indicate that over time this may increase to 48-78% of patients.[2] Compared to subjects in the general population, PD patients have a six-times higher risk to develop dementia.[3] Dementia severely reduces quality-of-life in PD of both the patient and caregiver, and is a major predictor of mortality and nursing home placement.[4] Several demographic and clinical features have been identified as risk factors for dementia in PD. Similar to findings in the general population, demographic features such as higher age and less education are associated with an increased risk of dementia in PD.[5-7] In addition, disease-related risk factors such as disease severity, age-at-onset, higher levodopa dose and use of anticholinergic drugs, have also been found related to the development of dementia in PD.[6-8] There are also indications that the predominant motor subtype is associated with dementia, as evidenced by the increased risk for patients with the Postural-Instability-and-Gait-Difficulty (PIGD) subtype, whereas dementia in tremor-dominant (TD) patients is relatively rare.[9] Additionally, several non-motor symptoms, including REM-sleep Behavior Disorder (RBD), depression and visual hallucinations, may be predictive of future development of dementia in PD.[2,6,10] Of note is that results from earlier studies on risk factors for dementia in PD have often yielded inconsistent results. For example, contrary findings have been reported for gender,[2,7] education,[2] age-at-onset,[2] disease duration,[6,11] Hoehn and Yahr stage,[6,11] depression,[6,11] and levodopa dose.[6,11] Apart from inconsistencies due to differences in populations, methodology, and outcome measures, lack of power in most studies is likely the major source of these conflicting results.[12] To identify risk factors for any outcome with some degree of certainty requires a large cohort that is followed sufficiently long for a significant number of subjects to develop the symptom of interest. Surprisingly, however, there are only few robust studies on this topic.[3,5,6] The SCOPA-PROPARK project is a longitudinal study of over 400 PD patients who have been examined annually and followed for five years (i.e., six assessments). The patients are broadly characterized and profiled on phenotype, genotype, disability and global outcomes of health.[13] These characteristics make this study well-suited for the purpose of identifying risk factors for the development of dementia in patients with PD. To our knowledge, this is the largest study on this topic so far. In this study both a cross-sectional and longitudinal approach is followed to identify potential risk factors for dementia in PD.

## METHODS

*Study Design and Participants*

Patients were recruited from neurology clinics of university and regional hospitals in the western region of the Netherlands and all fulfilled the United Kingdom Parkinson's disease Society Brain Bank criteria for idiopathic PD.[14] The majority of patients were evaluated at the Leiden University Medical Center, but more severely affected patients were offered the possibility to be examined at their homes to prevent selective drop-out. In view of the fact we aimed to obtain information on the full spectrum of the disease, a recruitment strategy based on age-at-onset (≤/>50 years) and disease duration (≤/>10 years) was applied. We intended to recruit at least 100 patients in each of the four strata.[13] The medical ethical committee of the Leiden University Medical Center approved the PROPARK study and written informed consent was obtained from all patients.[13]

*Ascertainment of dementia*

Cognitive function was assessed with the SCOPA-COG, a valid and reliable instrument that includes 10 items and examines four different cognitive domains: memory, attention, executive functioning, and visuospatial functioning.[13] The maximum score is 43, with higher scores reflecting better performance. A patient was considered to have dementia if a score of 22 was obtained; in an earlier study this cut-off value corresponded with the highest sum of sensitivity and specificity to diagnose dementia in patients with PD.[15]

*Assessment of Baseline Variables*

At baseline (2003-2005) and the five subsequent annual visits all patients received standardized assessments. The assessments included an evaluation of demographic and clinical characteristics, family history of PD, and registration of antiparkinsonian medication. A levodopa dose equivalent (LDE) of daily levodopa and dopamine agonists dose was calculated for each patient at baseline. The total LDE is the sum of levodopa dosage equivalent (LDE-Dopa) and the dopamine agonist dosage equivalent (LDE-DA).[16] Hoehn & Yahr (H&Y) stages of the patients were ascertained at every assessment.[17]

The following instruments were administered by qualified examiners: the SPES/ SCOPA[18] (including sections on motor examination, activities of daily living and motor complications), the SCOPA-COG (cognitive function),[13] and the SCOPA-PC (psychotic symptoms; items 1-5).[19] Over the years, there were in total five examiners, who all regularly attended retraining and recalibration sessions to prevent

inter-rater variability. All patients who used dopaminergic medication were assessed during “on’’. Patients completed the following instruments themselves: the SCOPA-AUT (three autonomic domains: gastrointestinal, urinary tract and cardiovascular),[20] the SCOPA-SLEEP (with sections on nighttime sleep problems [NS] and daytime sleepiness [DS]),[21] and the Beck Depression Inventory.[22] For all instruments except the SCOPA-COG, higher scores reflect poorer functioning. In addition, the association between presence of the APOEε4 allele (available for 272 patients) and dementia was examined in both the cross-sectional and longitudinal analyses.

*Statistical analysis*

Cross-sectional analyses were performed to assess differences at baseline between PD patients with and without dementia. Chi-square tests were used for comparing categorical variables, while independent t-tests were used for comparing normally distributed continuous variables. The Mann-Whitney U test was used if continuous variables were not normally distributed. A multivariate binary logistic regression analysis was subsequently performed to evaluate which variables contributed independently to dementia at baseline. Only patients who had no dementia at baseline were included in the longitudinal analysis. Additionally, patients who were only assessed at baseline and did not participate in later annual assessments were excluded from the longitudinal analysis.

In the longitudinal analyses we first examined univariate associations between individual baseline characteristics and future development of dementia using Cox regression. These baseline characteristics included: age, gender, education, age-at-onset, disease duration, H&Y stage, PIGD sumscore (sum of scores on items postural instability, gait, freezing and walking of the SPES-SCOPA; range 0-12), tremor sumscore (sum of scores of items rest and postural tremor of left and right hand of the SPES/SCOPA; range 0-12), sumscore of dyskinesias, sumscore of motor fluctuations, Beck Depression Inventory, presence of hallucinations (score 1 on item 1 of the SCOPA-PC), sumscore for autonomic dysfunction, sumscore for excessive daytime sleepiness (EDS), sumscore for nighttime sleep problems and the dosage of antiparkinsonian medication (total LDE, LDE-Dopa, LDE-DA).

All baseline variables with a p-value <0.10 from the univariate analyses were subsequently selected for inclusion in the multivariate Cox proportional hazards model to determine the independent contribution of these variables to the model. Variables were entered using a backward selection approach. Associations between baseline variables and development of dementia were calculated as hazard ratios (HR) with 95% confidence intervals (CI), with a HR > 1 indicating that the variable is associated with a higher risk of developing dementia.

*Calculation of survival time*

Follow-up ended at the date of final follow-up visit (for those still without dementia), the date of last examination before loss to follow-up, or the date of the examination at which dementia was documented, whichever came first. Survival time was calculated as the difference in years between these dates and the date of the patient's baseline assessment. Patients were considered to have an event ('uncensored') if they scored 22 or less on the SCOPA-COG. If a patient did not have an event during the complete follow-up, he or she was 'withdrawn alive' and classified as 'censored'. Additionally, if a patient died during follow-up, survival time was calculated as the difference between the date of the last assessment before death, and the date of the baseline assessment. If a patient had missed one year and had no dementia in the previous and following year, we assumed that the patient had not developed dementia in that year. In a secondary analysis, all analyses were repeated using the diagnostic cut-off value of the SCOPA-COG (17/18).[14]

Analyses were performed with the Statistical Package for the Social Sciences (SPSS) version 18.0.

**RESULTS**

Demographics and clinical characteristics of the study population at baseline are shown in Table 3.1.

*Cross-sectional analysis*

A total of 406 patients were included in the cross-sectional analysis (Figure 3.1). At baseline, 129 (31.8%) patients had dementia. Patients with dementia at baseline were older, had fewer years of education, longer disease duration, and an older age-at-onset (Table 3.1). Additionally, they were more severely affected on the H&Y scale, showed more severe depressive symptoms, had more autonomic dysfunction and daytime sleepiness, and more often suffered from hallucinations than non-demented patients. Patients with dementia also used higher doses of levodopa and dopamine agonists. With regard to motor symptoms, demented patients displayed a higher PIGD score and more severe dyskinesias. The proportion of APOEε4 carriers was not different between patients with and without dementia at baseline (24.3% versus 31.2%, respectively; p=0.275).

In the multivariate analysis, age, education, depression, hallucinations, and LDE-Dopa and LDE-DA were independently associated with presence of dementia at baseline. Application of the diagnostic cut-off value (17/18) resulted in 37 demented and 369 non-demented

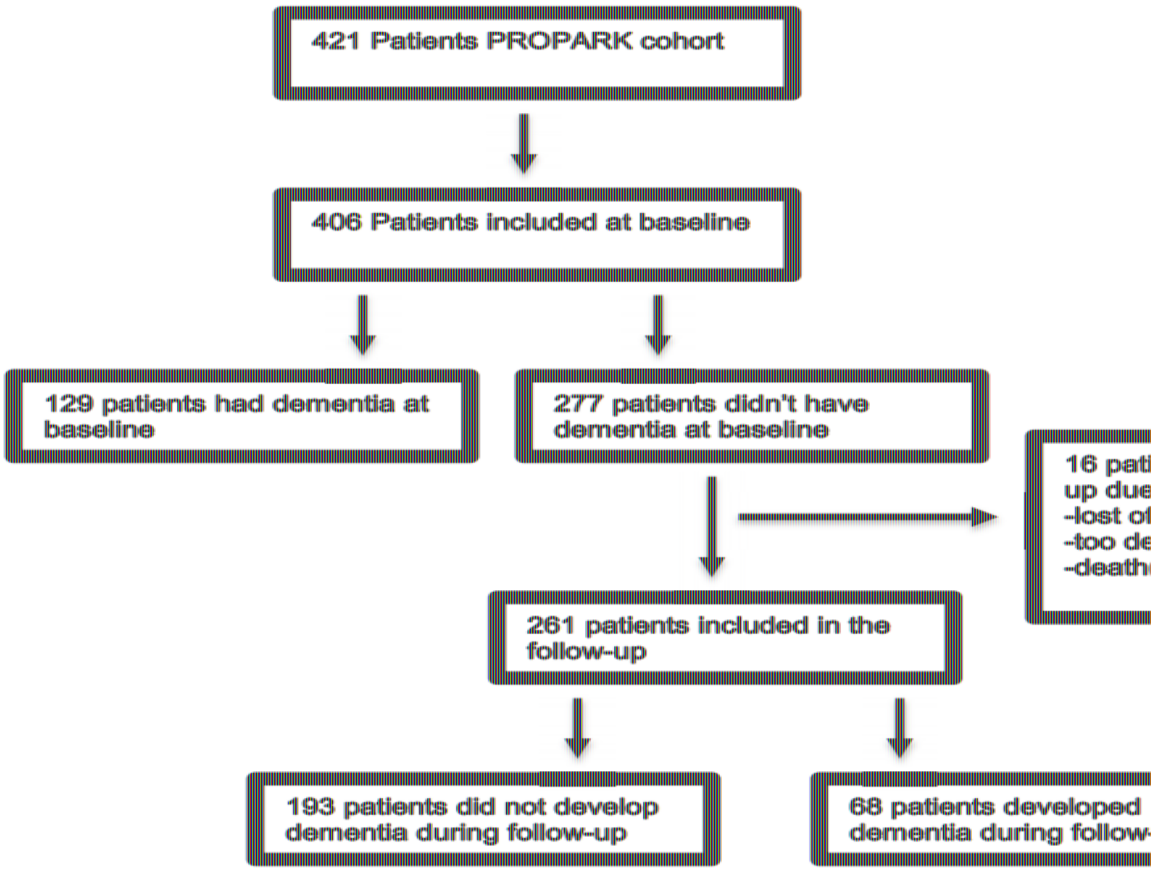
patients at baseline. In this analysis, the same variables were identified, except that dyskinesias and total LDE were not significant (Supplement 3.1, Table S3.1). In the multivariate analysis, age, education, depression and hallucinations were independently associated with the presence of dementia at baseline.

**Table 3.1:** Baseline data of patients with and without dementia

| | Total | With dementia | Without dementia | p-values |
|---|---|---|---|---|
| N | 406 | 129 | 277 | |
| Age, yr | 60.82 (11.23) | 66.46 (10.55) | 58.19 (10.57) | <0.001 |
| Sex, % male | 63.8 | 61.2 | 65.0 | 0.465[a] |
| DBS at baseline, % | 2.2 | 7.0 | 3.2 | 0.089[a] |
| Education, yr | 11.97 (4.10) | 10.27 (3.46) | 12.76 (4.14) | <0.001 |
| Age at onset, yr | 50.27 (11.84) | 54.39 (11.75) | 48.36 (11.41) | <0.001 |
| Disease duration, yr | 10.14 (6.20) | 12.08 (6.87) | 9.84 (6.24) | 0.001 |
| Hoehn & Yahr, stage | 2 (2,3) | 3 (2,4) | 2 (2,3) | <0.001[b] |
| Tremor score | 3.66 (1.99) | 3.55 (2.10) | 3.70 (1.94) | 0.482 |
| PIGD score | 2.32 (1.88) | 3.27 (2.18) | 1.88 (1.53) | <0.001 |
| Dyskinesia score | 0.93 (1.61) | 1.35 (1.87) | 0.74 (1.45) | 0.001 |
| Motor Fluctuations | 0.78 (1.26) | 0.82 (1.32) | 0.77 (1.23) | 0.723 |
| Beck Depression Inventory | 10.09 (6.53) | 12.47 (7.65) | 9.00 (5.63) | <0.001 |
| SCOPA-COG | 25.60 (6.28) | 18.32 (3.54) | 28.99 (3.97) | <0.001 |
| MMSE-score | 26.73 (2.71) | 24.61 (3.00) | 27.71 (1.89) | <0.001 |
| SCOPA-SLEEP, nighttime | 4.52 (3.76) | 4.17 (3.52) | 4.68 (3.86) | 0.213 |
| SCOPA-SLEEP, EDS | 4.83 (3.72) | 5.79 (3.80) | 4.39 (3.60) | <0.001 |
| SCOPA-AUT, total score | 10.53 (5.70) | 12.96 (6.32) | 9.42 (5.02) | <0.001 |
| Hallucinations, % with | 16.3 | 27.4 | 11.3 | <0.001[a] |
| Total LDE, mg/day | 608 (466) | 709 (458) | 561 (463) | 0.003 |
| LDE-Dopa, mg/day | 379 (378) | 514 (395) | 316 (354) | <0.001 |
| LDE-DA dose, mg/day | 232 (226) | 196 (210) | 248 (232) | 0.031 |

*Variables are expressed as means (standard deviations), except for gender (percentages), and Hoehn and Yahr stage (median ((interquartile range)). All differences are calculated with the independent-samples t-tests, except for [a]Chi-square test and [b]Mann-Whitney U test.*
*DBS: Deep Brain Surgery.*
*MMSE: Mini-mental state examination, higher scores reflect better functioning;*
*SCOPA-COG: cognitive function, higher scores reflect better functioning;*
*SCOPA-SLEEP, nighttime: nighttime sleep problems; SCOPA-SLEEP, EDS: daytime sleepiness;*
*SCOPA-AUT, total score: sumscore autonomic functioning including items from the sections on gastrointestinal, cardiovascular and urinary tract; LDE: Levodopa dosage equivalent; DA: Dopamine agonists; PIGD: Postural Instability Gait Difficulty.*

**Figure 3.1:** Flow Chart of follow-up for dementia



*Longitudinal analysis*

A total of 277 patients did not have dementia at baseline; of these, 16 patients were lost to follow-up during the first year due to death (n=1), loss of interest (n= 9) or the fact that they considered the study too demanding (n=6). Thus 261 patients without dementia at baseline were followed with a mean (standard deviation[SD]) follow-up time of 4.83 (0.81) years. Sixty-eight (26.1%) of these patients, of which 49 were men, developed dementia after a mean (SD) follow-up time of 2.56 (1.42) years (Supplement 3.1 Figure S3.1). In total 48 patients (of whom 16 died) were lost to follow-up in the longitudinal analysis. Patients lost to follow-up were older at time of examination (64.64 [11.48] vs 56.84 [9.88]; $p < 0.001$), had a higher age of onset disease (54.72 [11.77] vs 47.02 [10.89]; $p < 0.001$), had higher depression scores (11.42 [7.71] vs 8.49 [4.97]; p=0.014), lower SCOPA-COG score (27.38 [3.82] vs 29.32 [3.93]; p=0.002) and had more severe PIGD symptoms (2.50 [1.92] vs 1.75 [1.41]; p=0.015). No statistical significant differences were found for any of the other variables. Univariate analyses showed a significant relation between development of dementia and age, education, age-at-onset, disease duration, H&Y, total LDE, LDE-Dopa dose, EDS, autonomic dysfunction, depression and presence of hallucinations. Of the motor symptoms, PIGD and dyskinesias - but not tremor or motor fluctuations - were significantly related to the outcome. No relation was found between presence of the APOEε4 allele and risk of dementia (HR=1.574, 95% CI: 0.901-2.750; p=0.111). (Table 3.2)

Twelve of the 14 baseline variables with a p-value <0.10 were entered in the multivariate Cox proportional hazards' model. Age-at-onset was not included because it is determined by age and disease duration, while total LDE was not included because it is partly determined by daily levodopa dose; inclusion of these variables would have led to collinearity and, consequently, inaccurate results. Older age at baseline, fewer years of education, higher daily levodopa dose and EDS emerged as independent risk factors for dementia in our population (Table 3.3).

Application of the diagnostic cut-off value (17/18) showed that of the 369 patients who were not demented at baseline, 59 (16.0%) developed dementia during follow-up. In this analysis, the same variables were identified as at the optimal cut-off value, except that education and hallucinations were no longer significant, whereas motor fluctuations now showed a significant association with dementia (Supplement 3.2 Table 3.2). In the multivariate analysis, age, depression, EDS, levodopa dose and H&Y stage were independently associated with the presence of dementia risk.

**Table 3.2:** Univariate associations between baseline characteristics and risk of developing dementia

| | Hazard Ratio (95% CI) | p-values |
|---|---|---|
| Age, p/yr increase | 1.100 (1.073-1.127) | <0.001 |
| Sex, HR for males[a] | 1.469 (0.865-2.497) | 0.155 |
| DBS Surgery at baseline, yes/no[b] | 0.399 (0.145-1.099) | 0.075 |
| Education, p/yr increase | 0.867 (0.805-0.933) | <0.001 |
| Age at onset, p/yr increase | 1.059 (1.037-1.083) | <0.001 |
| Disease duration, p/yr increase | 1.062 (1.029-1.097) | <0.001 |
| Hoehn & Yahr, p/stage increase | 1.635 (1.237-2.160) | 0.001 |
| Tremor score, p/point increase | 1.031 (0.918-1.159) | 0.602 |
| PIGD score, p/point increase | 1.371 (1.184-1.588) | <0.001 |
| Dyskinesia score, p/point increase | 1.180 (1.031-1.351) | 0.016 |
| Motor Fluctuations, p/point increase | 1.038 (0.860-1.253) | 0.695 |
| Beck Depression Inventory, p/point increase | 1.039 (1.005-1.075) | 0.026 |
| SCOPA-SLEEP – nighttime, p/point increase | 1.031 (0.970-1.095) | 0.325 |
| SCOPA-SLEEP – EDS, p/point increase | 1.115 (1.050-1.184) | <0.001 |
| SCOPA-AUT, total score p/point increase | 1.106 (1.058-1.155) | <0.001 |
| Presence of hallucinations, | 2.173 (1.185-3.985) | 0.012 |
| Total LDE, p/point increase | 1.001 (1.000-1.001) | 0.002 |
| Daily Levodopa Dose, p/100 mg increase | 1.153 (1.094-1.216) | <0.001 |
| Daily DA Dose, p/100 mg increase | 0.933 (0.837-1.041) | 0.216 |

*All variables are expressed as hazard ratio (HR) with 95% confidence interval (CI). EDS: Excessive Daytime Sleepiness; PIGD: Postural Instability Gait Difficulty; LDE: Levodopa dosage equivalent; DA: Dopamine agonists.*
*[a]HR for developing dementia for male versus female patients.*
*[b]HR for developing dementia for patients who had Deep brain surgery(DBS) at baseline versus those who didn't.*

**Table 3.3:** Multivariate Cox proportional hazards model of risk factors for dementia in Parkinson's disease

| | Hazard Ratio (95% CI) | P-values |
|---|---|---|
| Age, yr | 1.082 (1.054-1.111) | <0.001 |
| Education, yr | 0.900 (0.837-0.968) | 0.004 |
| SCOPA-SLEEP - EDS | 1.073 (1.002-1.148) | 0.042 |
| Daily Levodopa Dose, p/100mg increase | 1.122 (1.048-1.203) | 0.001 |
| Disease duration, yr | 1.008 (0.958-1.060) | 0.760 |
| Hallucinations, presence vs absence | 1.559 (0.774-3.137) | 0.214 |
| Autonomic dysfunction | 0.982 (0.928-1.039) | 0.534 |
| PIGD score | 1.044 (0.823-1.325) | 0.723 |
| Hoehn & Yahr stage | 1.169 (0.837-1.632) | 0.360 |
| Dyskinesia score | 0.972 (0.791-1.194) | 0.785 |
| Beck Depression Inventory | 1.034 (0.987-1.084) | 0.159 |
| Total LDE, p/point increase | 0.999 (0.998-1.000) | 0.143 |
| DBS Surgery, yes/no | 0.798 (0.161-3.952) | 0.782 |

*All variables are expressed with hazard ratio (HR) with 95% confidence interval.*
*EDS: Excessive Daytime Sleepiness; PIGD: Postural Instability Gait Difficulty; LDE: Levodopa dosage equivalent; DA: Dopamine agonists. DBS: Deep Brain surgery.*

## DISCUSSION

We identified risk factors for dementia in a cohort of over 400 patients with PD who have been followed up to five years. A total of 129 (31.8%) patients already had dementia at the start of the study. Demographic risk factors that were associated with baseline dementia included higher age and fewer years of education, while disease-related and clinical factors that were associated with dementia at baseline involved disease duration, age-at-onset, levodopa use, H&Y stage, PIGD score, dyskinesia, EDS, autonomic dysfunction, depression and the presence of hallucinations. The longitudinal analysis showed that 68 (26.1%) patients who had no dementia at baseline developed dementia during follow-up. Results from the longitudinal analysis corresponded with those of the cross-sectional analysis except for the dose of dopamine agonists, which was only found significant in the cross-sectional analysis. In addition, results obtained with the diagnostic cut-off value of the SCOPA-COG (17/18) corresponded with those of the optimal cut-off value (22/23), except for a few minor differences. Only 48 patients (17.3%) were lost to follow-up; these patients were older, had a higher age of onset disease, were more depressed, had more cognitive impairment and more severe PIGD than patients who continued to participate. Since all these variables were found associated with development of dementia, hazard ratios may have been underestimated, but not overestimated. We found no relation between the presence of an APOEε4 allele and dementia, neither at baseline nor during follow-up, which is in line with the results of larger and more rigorously conducted studies.[23-25] There have been studies that found a positive relation between APOEε4 allele frequency and PDD, but these are generally small.[26] In addition, a meta-analysis reported a marginally increased odds ratio of 1.6 (95% CI: 1.0-2.6), but found indications of publication bias, especially with respect to the APOEε4 allele.[27] Risk factors that were reported in earlier studies that were confirmed in the present study include older age and age-at-onset, fewer years of education, longer disease duration, higher total levodopa dose, higher H&Y stage, higher PIGD score, EDS, autonomic dysfunction, depression and the presence of hallucinations.[2,11] Male gender is sometimes identified as a risk factor for dementia in PD,[7] but, in agreement with most studies, we found no significant role of gender in our cohort. A risk factor that has not been reported in earlier studies is the severity of dyskinesias. A plausible explanation is that dyskinesias are associated with longer duration of levodopa treatment and hence with longer disease duration and a higher risk of dementia. However, recent evidence also indicates that pathophysiological mechanisms underlying levodopa-indicated dyskinesias are associated with cortical morphological and functional alterations within the prefrontal cortex[28] and, given that a loss of dopaminergic activity in the frontal lobe and the prefrontal cortex are well-known markers of cognitive decline as reported in imaging studies,[29] this may suggest a pathophysiological link between dyskinesias and PD dementia (PDD). Additionally, the

inferior frontal cortex and supplementary motor area, two regions involved in executive control, have also been shown to play an important role in response inhibition[30] and imaging studies showed that lesions to these regions are associated with mild cognitive impairment.[28] Moreover, a higher frequency of impulse control disorders has been found in patients with dyskinesias compared to patients without dyskinesias.[31] Together these data suggest that dyskinesias, mild cognitive impairment and impulse control disorders are pathophysiologically related in PD. In the prospective multivariate model, age, education, daily levodopa dosage and EDS emerged as independent risk factors for developing dementia. One might have expected that 'usual suspects' such as disease duration, and H&Y stage or PIGD, would also have emerged as independent risk factors, but these factors apparently shared too much variance with age, EDS and daily levodopa dose to make a significant independent contribution. Although we consider the results from the Cox proportional hazard analysis at the optimal cut-off value (22/23) as the main result of this study, the other analyses can be used to verify the robustness of our findings. If we consider the variables that have been identified in the four multivariate models (i.e., cross-sectional and longitudinal models at two different cut-off values) we notice that age emerges in all four models, while education, depression and levodopa dose are present in three models, hallucinations and EDS in two models, and that LDE-DA and H&Y are present in only one model. Higher age, a lower level of education and depression are general risk factors for dementia and, in this perspective, not specific to PD. Nevertheless, the role of age in PD and in the onset of PDD is complicated; although higher age in general is a risk factor for dementia, higher age in PD is associated with a much higher risk of dementia than the effect of age alone, indicating that there is an interactive effect of age and PD severity on the risk of dementia.[32] Given that higher age in PD will also be associated with disease duration, it is difficult to disentangle the effects of age and disease duration on the risk of dementia in PD. PD-related variables that emerged repeatedly in the multivariate models included levodopa dose, hallucinations and EDS, and the potential role of these features in the development of PDD warrants further discussion. Although we found that the presence of hallucinations is a potential predictor of dementia, it should be considered that the reverse relation also exists; more cognitive impairment at baseline is also associated with future development of hallucinations.[33] Findings from pathological studies in PD indicate that visual hallucinations and dementia may share limbic pathology.[34] Previous longitudinal studies have shown that EDS is a risk factor for cognitive decline and dementia, both in the general population and in patients with PD.[35,36] EDS may even antedate the onset of PD.[37] Possible explanations for the occurrence of EDS include the fact that a decrease in dopamine in PD could potentially be responsible for excessive daytime napping due to the arousal-related role of dopamine.[37] In addition, impaired wakefulness in PD may reflect neuronal loss and Lewy body

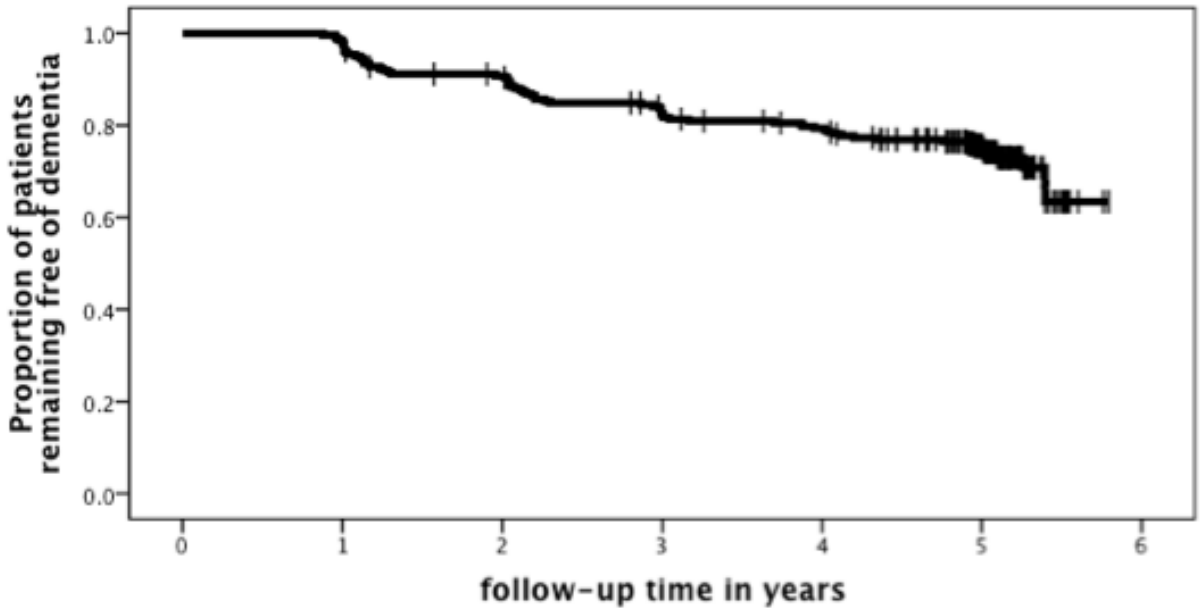
accumulation in the brainstem, basal forebrain regions, hypothalamus, and thalamus and accompanying neurochemical alterations in cholinergic, monoaminergic, dopaminergic, and histaminergic systems or the modulatory orexin/hypocretin systems.[38] Interestingly, similar neuroanatomical regions and neurotransmitter systems to those involved in sleep-wake regulation are implicated in the cognitive domains of attention, executive function, learning, and memory,[35,38-40] which may explain why the two constructs are related. We also found that non-demented patients with a higher PIGD score at baseline were at higher risk of developing dementia during follow-up, but that the tremor score was not significantly associated with future development of dementia, neither at baseline nor during follow-up. We previously argued[13] that the differential relation of PIGD and tremor with cognition casts doubt on the rationale of combining these two scores in a ratio (as is often done), where the tremor score is divided by the PIGD score. Combining these two scores into a ratio only makes sense if the two are related, or if there is some kind of trade-off between them. In this case, however, the risk is only conveyed by the denominator (i.e., PIGD), not the numerator (i.e., tremor). Indeed, when the effect of tremor on dementia is studied separately, usually no relation is found.[39] In contrast, studies that reported that patients with a tremor dominant subtype have a reduced risk of developing dementia, usually applied a ratio to classify patients.[9] It is plausible that in these cases it is in fact the low PIGD score that classifies patients as tremor dominant; with advancing disease, the PIGD score usually increases much more sharply than the tremor score which does not increase at all or only slightly, causing a “switch of motor type” with inherent increased risk of developing dementia. Our argumentation is further supported by the much stronger relation of disease duration and H&Y stage with the PIGD score (r=0.32 and 0.75 at baseline, respectively), than with the tremor score (r=0.12 and r=0.06 at baseline, respectively). That autonomic dysfunction emerged as a risk factor was not unexpected. Neuropathological studies provided evidence that α-synuclein deposits in the dorsal IX an X motor nucleus and lower brainstem are already found in Braak stage 1.[41] Other studies showed that the enteric nervous system of stomach and gut may be affected even earlier.[42] Clinical studies indeed show that autonomic symptoms generally occur early in the disease,[43] and therefore precede the development of dementia. Interestingly, in the present study we used items from three sections of the SCOPA-AUT, i.e., gastrointestinal symptoms, urinary tract symptoms and cardiovascular symptoms, and found in the univariate analyses that not only the total score, but also the three separate scores were significantly associated with future development dementia (data not shown). Many of the other risk factors we identified, such as longer disease duration, higher total levodopa dose, more severe dyskinesias, depression and higher H&Y stage, represent variables that are markers of more advanced disease, indicating that these patients are closer in time to milestones that develop even later in the disease course (e.g.,

dementia). One of the limitations of our study is the fact that we were not able to verify the relationship between some potential risk factors and the development of dementia, because these variables were not evaluated at baseline when this study was initiated in 2003. For example, RBD is a well-documented risk factor for dementia in PD reported in earlier studies,[9,11] but was not included here. Another issue is the potential bias caused by the misclassification of dementia status in some patients, due to the fact that we did not employ the gold standard for diagnosing dementia in PD, i.e., the Movement Disorder Society criteria for the diagnosis of Parkinson's disease dementia.[39] However, we have no reasons to assume that any potential misclassification is systematic, and, given that non-differential misclassification of a dichotomous variable will always bias the effect, if there is one, towards the null value, some effects may have been underestimated, but not overestimated. A third point that should be considered is the fact that our study is hospital-based and not community-based, and that we applied a pre-stratification strategy based on age-at-onset and disease duration. This may have affected the prevalence of dementia and the prevalence or severity of certain symptoms, but the objective of this study was not to calculate the incidence proportion of dementia, but to identify risk factors for dementia. These latter are based on internal comparisons of those recruited. We cannot rule out that the increase in variation in age-at-onset and disease duration caused by our sampling strategy may have affected the strengths of the identified relations to some extent if compared to what would have been found in a population-based sample; however, the relations between dementia and most of the risk factors are so strong that it is hardly conceivable that any selection bias may have resulted in variables that we have identified as significant, that would be non-significant in an unselected population. In addition, the fact that largely the same factors were identified in both the cross-sectional and longitudinal analysis - which involved different PDD patients - further supports the credibility of our findings. Finally, we were not able to examine which variables were associated with future development of mild cognitive impairment (MCI). This is due to the fact that diagnostic criteria for PD-MCI were not available at the time the data of this study were collected (i.e., between 2003 and 2009), while the PD-MCI criteria were not published until 2012.[44] Retrospective application of the MCI criteria to our data was not possible because we did not collect information on two criteria essential to the diagnosis of MCI, namely: that there is ‘gradual decline, in the context of established PD, in cognitive ability’; and that ‘cognitive deficits are not sufficient to interfere significantly with functional independence’ (which, for example, is evaluated by examining the patient's ability to manage finances or medication). Strong points of this study are the large number of patients, the longitudinal design, the broad characterization of the patients with valid and reliable instruments, the long duration of follow-up and the low number of patients that were lost to follow-up. To summarize, the

onset of dementia in PD involves a combination of potentially interacting risk factors that are associated with higher age and more advanced disease. Motor symptoms such as PIGD and dyskinesias and non-dopaminergic symptoms such as autonomic dysfunction, EDS, hallucinations and depression are predictors of the development of dementia in patients with PD. This indicates that patients with these characteristics must be examined carefully for the presence of early signs of dementia, while a more frequent follow-up of these patients should be considered.

**SUPPLEMENT 3.1**

**Figure S3.1:** Kaplan Meier Curve showing the proportion of patients surviving without dementia




Of the 277 patients who did not have dementia at baseline, 16 died during follow-up. Death causes were known for 8 patients and were not PD-related.
The annual progression to dementia is as follows:
Between 1st and 2nd year: 23 of 277 at risk (8.30%)
Between 2nd and 3rd year: 16 of 238 at risk (6.72%)
Between 3rd and 4th year: 10 of 216 at risk (4.63%)
Between 4th and 5th year: 11 of 202 at risk (5.45%)
Between 5th and 6th year: 8 of 169 at risk (4.73%)
The average percentage of patients progressing to dementia per year is: 5.97.

— *survival curve* + *event (develops dementia)*

**Table S3.1:** Baseline data of patients with and without dementia (using the diagnostic cut-off value of 17/18)

| | Total | With dementia | Without dementia | P-values |
|---|---|---|---|---|
| N | 406 | 37 | 369 | |
| Age, yr | 60.82 (11.23) | 70.63 (7.28) | 58.19 (10.57) | <0.001 |
| Sex, % male | 63.8 | 54.1 | 64.8 | 0.196[a] |
| DBS at baseline, % | 4.4 | 5.4 | 4.3 | 0.763[a] |
| Education, yr | 11.97 (4.10) | 9.42 (3.12) | 12.22 (4.10) | <0.001 |
| Age at onset, yr | 50.27 (11.84) | 57.84 (9.29) | 49.51 (11.81) | <0.001 |
| Disease duration, yr | 10.55 (6.53) | 12.80 (8.06) | 10.32 (6.32) | 0.028 |
| Hoehn & Yahr, stage | 2 (2,3) | 3 (2,4) | 2 (2,3) | <0.001[b] |
| Tremor score | 3.66 (1.99) | 3.85 (2.17) | 3.64 (1.98) | 0.563 |
| PIGD score | 2.32 (1.88) | 3.69 (2.25) | 2.18 (1.78) | <0.001 |
| Dyskinesia score | 0.93 (1.61) | 1.33 (1.88) | 0.89 (1.58) | 0.183 |
| Motor Fluctuations | 0.78 (1.26) | 0.82 (1.32) | 0.77 (1.23) | 0.702 |
| Beck Depression Inventory | 10.09 (6.53) | 13.81 (7.66) | 9.73 (6.31) | <0.001 |
| SCOPA-COG | 25.60 (6.28) | 13.76 (2.87) | 26.78 (5.21) | <0.001 |
| MMSE-score | 26.73 (2.71) | 22.50 (3.47) | 27.14 (2.24) | <0.001 |
| SCOPA-SLEEP, nighttime | 4.52 (3.76) | 4.33 (3.56) | 4.54 (3.78) | 0.759 |
| SCOPA-SLEEP, EDS | 4.83 (3.72) | 6.41 (3.29) | 4.67 (3.72) | 0.007 |
| SCOPA-AUT, total score | 10.53 (5.70) | 12.21 (5.73) | 10.37 (5.68) | 0.078 |
| Hallucinations, % with | 16.3 | 41.7 | 13.8 | <0.001[a] |
| Total LDE, mg/day | 608 (466) | 661 (378) | 603 (474) | 0.469 |
| LDE-Dopa, mg/day | 379 (378) | 514 (395) | 316 (354) | 0.023 |
| LDE-DA dose, mg/day | 232 (226) | 148 (183) | 240 (229) | 0.018 |

*Variables are expressed as means (standard deviations ), except for gender (percentages), and Hoehn and Yahr stage (median ((interquartile range)). All differences are calculated with the independent-samples t-tests, except for [a] Chi-square test and [b] Mann-Whitney U test.*

*DBS: Deep Brain Surgery MMSE: Mini-mental state examination, higher scores reflect better functioning; SCOPA-COG: cognitive function, higher scores reflect better functioning; SCOPA-SLEEP, nighttime: nighttime sleep problems; SCOPA-SLEEP, EDS: daytime sleepiness; SCOPA-AUT, total score: sumscore autonomic functioning including items from the sections on gastrointestinal, cardiovascular and urinary tract; LDE: Levodopa dosage equivalent; DA: Dopamine agonists; PIGD: Postural Instability Gait Difficulty.*

**SUPPLEMENT 3.2**

**Table S3.2:** Univariate associations between baseline characteristics and risk of dementia (using diagnostic cut-off value of 17/18)

| | Hazard Ratio (95% CI) | P-value |
|---|---|---|
| Age, p/yr increase | 1.109 (1.080-1.139) | <0.001 |
| Sex, HR for males[a] | 1.466 (0.834-2.576) | 0.184 |
| DBS Surgery at baseline, yes/no[b] | 0.865 (0.393-1.907) | 0.865 |
| Education, p/yr increase | 0.934 (0.871-1.002) | 0.058 |
| Age at onset, p/yr increase | 1.064 (1.041-1.088) | <0.001 |
| Disease duration, p/yr increase | 1.066 (1.029-1.104) | <0.001 |
| Hoehn & Yahr, p/stage increase | 2.368 (1.791-3.130) | <0.001 |
| Tremor score, p/point increase | 1.066 (0.941-1.208) | 0.312 |
| PIGD score, p/point increase | 1.521 (1.350-1.713) | <0.001 |
| Dyskinesia score, p/point increase | 1.259 (1.101-1.439) | 0.001 |
| Motor Fluctuations, p/point increase | 1.251 (1.042-1.502) | 0.016 |
| Beck Depression Inventory, p/point increase | 1.065 (1.033-1.097) | <0.001 |
| SCOPA-SLEEP – nighttime, p/point increase | 1.004 (0.938-1.074) | 0.910 |
| SCOPA-SLEEP – EDS, p/point increase | 1.099 (1.034-1.169) | 0.003 |
| SCOPA-AUT, total score p/point increase | 1.147 (1.100-1.197) | <0.001 |
| Presence of hallucinations, yes/no | 1.617 (0.835-3.132) | 0.154 |
| Total LDE, p/point increase | 1.001 (1.000-1.001) | <0.001 |
| Daily Levodopa Dose, p/100 mg increase | 1.176 (1.111-1.244) | <0.001 |
| Daily DA Dose, p/100 mg increase | 0.955 (0.852-1.070) | 0.427 |

*All variables are expressed as hazard ratio (HR) with 95% confidence interval (CI). EDS: Excessive Daytime Sleepiness; PIGD: Postural-instability-gait disorder; LDE: Levodopa dosage equivalent; DA: Dopamine agonists.*

*[a]HR for developing dementia for male versus female patients.*
*[b]HR for developing dementia for patients who had Deep brain surgery(DBS) at baseline versus those who didn't.*

***Multivariate Analysis shows:***
*Hoehn and Yahr (HR=1.448, 95% CI: 1.048-2.001; p=0.025)*
*EDS (HR=1.068, 95% CI: 1.003-1.138; p=0.039)*
*Depression (HR=1.067, 95% CI: 1.026-1.110; p=0.001)*
*Daily levodopa dosage (HR=1.001, 95% CI: 1.001-1.002; p=0.001)*
*Age (HR=1.104, 95% CI: 1.071-1.138; p<0.001)*

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Chapter 4:

# Course and risk factors for excessive daytime sleepiness in Parkinson's disease


Kangdi Zhu[1]; Jacobus J. van Hilten[1]; Johan Marinus[1]

[1]Department of Neurology, Leiden University Medical Center, Leiden, The Netherlands

Published in *Parkinsonism and Related Disorders* 2016;24:34-40

**ABSTRACT**

*Introduction.* Excessive daytime sleepiness (EDS) is a common feature of Parkinson's disease (PD) that contributes to the disease burden and increases risk of harm. The aim of this study was to examine persistency, cross-sectional and longitudinal associations, and risk factors for EDS in patients with PD. *Methods.* Analyses were performed on data from the SCOPA-PROPARK cohort, a 5-year hospital-based longitudinal cohort of over 400 PD patients who were examined annually. Cross-sectional analyses were conducted to evaluate differences between patients with and without EDS at baseline, while linear mixed models using data of all patients were used to identify factors associated with longitudinal changes in SCOPA-SLEEP-Daytime Sleepiness (SCOPA-SLEEP-DS) scores. A survival analysis was done using data of patients without EDS at baseline to identify risk factors for future EDS. *Results.* EDS proved a non-persistent symptom, although persistency and the proportion of patients with EDS increased with longer follow-up. At baseline 43% of patients had EDS, while 46% of patients without EDS at baseline developed this symptom during follow-up. Male gender, poorer nighttime sleep, cognitive and autonomic dysfunction, hallucinations, less severe dyskinesias, dose of dopamine agonists and use of antihypertensives were associated with higher EDS scores over time, while use of benzodiazepines was associated with lower scores. Baseline SCOPA-SLEEP-DS score and PIGD phenotype were risk factors for future EDS. *Conclusions.* With longer disease duration a large proportion of patients develop EDS. Some risk factors are modifiable and patients should be monitored to improve quality of life and reduce risk of harm.

## INTRODUCTION

Excessive daytime sleepiness (EDS) is a common feature of Parkinson's disease (PD), which can affect up to 50% of patients.[1] The American Academy of Sleep Medicine defines EDS as the inability to maintain wakefulness and alertness during the major waking episodes of the day, with sleep occurring unintentionally or at inappropriate times almost daily for at least three months.[2] EDS in PD contributes significantly to the disease burden, and increases the risk of harm to patients.[3] Understanding the risk factors for EDS may help to prevent, identify, and target interventions to the correct patients. Earlier studies found that the presence of EDS is associated with dopamine agonist (DA) use, higher age, male gender, advanced disease, the postural-instability-gait-difficulty (PIGD) motor phenotype, insomnia, hallucinations, cognitive decline and depression.[4,5] Information on the relation between EDS and the use of medications such as antidepressants, antihypertensives and benzodiazepines, which are known to cause sleepiness in the general population, is scarce in PD.[6,7] The results on associated variables and predictors for EDS from previous studies were often inconsistent, likely due to small sample sizes and methodological differences between these studies.[4,5] Furthermore, most previous studies on EDS in PD had a cross-sectional design and to date only two longitudinal studies have been performed.[4,5] One study (n=131) showed that 23% of patients who were free of EDS developed this feature during a four year follow-up period and that the presence of EDS was associated with more severe disability and cognitive impairment. Although this study had a longitudinal setup, data of patients with EDS at baseline were pooled with those who developed EDS during follow-up, after which they were compared to those of patients who had no EDS at both time points. This strategy therefore actually involved a cross-sectional comparison and the data provide limited information on features that are related to changes in EDS over time.[5] The other study (n=153) - performed in early, initially drug naïve patients - found that the occurrence of EDS increases with disease progression and that its presence is not a persistent feature but instead may fluctuate over time; they further found that EDS severity is associated with male gender, depression, ADL disability and DA use.[4] Large longitudinal studies on EDS in more advanced PD are lacking. The PROPARK cohort study includes over 400 PD patients who have been examined annually and followed for five years (i.e., six assessments), which makes this study very well-suited for the purpose of identifying factors associated with (the development of) EDS in PD.

## METHODS

*The PROPARK cohort*

Patients were recruited from neurology clinics of university and regional hospitals in the western part of the Netherlands and all fulfilled the United Kingdom Parkinson's disease Society Brain Bank criteria for idiopathic PD.[8] The majority of patients were evaluated at the Leiden University Medical Center, but more severely affected patients were offered the possibility to be examined at their homes to prevent selective drop-out. In view of the fact we aimed to obtain information on the full spectrum of the disease, a recruitment strategy based on age-at-onset (< or ≥50 years) and disease duration (< or ≥10 years) was applied. We intended to recruit at least 100 patients in each of the four strata.[9] The medical ethical committee of the Leiden University Medical Center approved the PROPARK study and written informed consent was obtained from all patients.[9]

*Measures and assessments*

At baseline (2003-2005) and the five subsequent annual visits all patients received standardized assessments. These included an evaluation of demographic and clinical characteristics, family history of PD, and registration of antiparkinsonian medication. A levodopa dose equivalent (LDE) of daily levodopa and dopamine agonists dose was calculated for each patient at baseline. The total LDE is the sum of the levodopa dosage equivalent (LDE-Dopa) and the dopamine agonist dosage equivalent (LDE-DA).[10] Diagnosis and Hoehn & Yahr (H&Y) stages of the patients were ascertained at every assessment.[11] The following instruments were administered by qualified examiners: the SPES/SCOPA (including sections on motor examination, activities of daily living and motor complications),[12] the SCOPA-COG (cognitive function),[9] and the SCOPA-PC[13] (psychotic symptoms; items 1-5). Over the years, there were in total five examiners, who all regularly attended retraining and recalibration sessions to prevent inter-rater variability. All patients who used dopaminergic medication were assessed during “on’’. Patients completed the following instruments themselves: the SCOPA-AUT (three autonomic domains: gastrointestinal, urinary tract and cardiovascular),[14] the SCOPA-SLEEP (with sections on nighttime sleep problems [NS] and daytime sleepiness [DS]),[15] and the Beck Depression Inventory (BDI).[16] For all instruments except the SCOPA-COG, higher scores reflect poorer functioning. Patients were classified according to motor subtype using a ratio of tremor score (SPES/SCOPA) over PIGD score (SPES/SCOPA).[9,17] A total tremor or PIGD score of 0 was replaced by 0.5. Patients with a ratio value <1.0 were classified as PIGD dominant, whereas those with values from 1.0 were classified as non-PIGD dominant.[9,17]

*Ascertainment of excessive daytime sleepiness*

EDS was assessed using the daytime sleepiness (DS) section of the SCOPA-SLEEP questionnaire.[15] The SCOPA-SLEEP-DS evaluates daytime sleepiness in the past month, and includes six items with four response options [0 (never) to 3 (often)], with a maximum score of 18 and mainly focuses on falling asleep in unexpected or unwanted situations. Patients were considered to suffer from EDS if they scored 5, according to earlier suggested cut-offs.[15]

*Statistical analysis*

The objectives of the analyses of this study are: 1) to examine which factors are associated with the presence of EDS; 2) to evaluate which variables are associated with longitudinal variation in EDS scores; and 3) to identify risk factors for future development of EDS. To this end we first evaluated which features were associated with the presence of EDS in the baseline data of our population (objective 1). For objective 2 a linear mixed models (LMM) analysis was performed using data of all patients included in the follow-up. This method allows for the identification of variables that are associated with variation in SCOPA-SLEEP DS scores over time. LMM takes into account that repeated measures in the same subject are not independent but correlated. Baseline variables that have been found associated with EDS in earlier studies were considered in the LMM. These included: age, gender, disease duration, sumscore of motor impairment and activities of daily living (SPES/SCOPA), motor phenotype, presence of hallucinations (score 1 on item 1 of the SCOPA-PC), scores on autonomic dysfunction (gastro-intestinal, urinary tract and cardiovascular domains), sumscore for nighttime sleep problems, sumscore of BDI, sumscore of cognitive dysfunction (SCOPA-COG) and dosage of antiparkinsonian medication (LDE-Dopa, LDE-DA). A few other variables were added because a relation with development of EDS could be presumed: sumscore of dyskinesias, sumscore of motor fluctuations and the use of benzodiazepines or antihypertensives. The LMM was first executed with only one independent variable at a time (unadjusted model). Hereafter an adjusted model that considers the main effects of all baseline variables was performed. The final model only includes the variables that were significant from the unadjusted and the adjusted model. To examine which characteristics were associated with future development of EDS (objective 3), we performed a survival analysis in the data of patients who had no EDS at baseline, using the same variables that were considered in the LMM. We also added the baseline SCOPA-SLEEP DS score in this analysis, since it may be an important determinant for developing EDS.[4] For each variable a hazard ratio (HR) with 95% confidence intervals (CI) was calculated, with a HR > 1 indicating that this variable is associated with a higher risk of developing EDS. If for a particular patient 25% or more of the items of a scale was missing,

the patient was excluded from statistical analyses (this occurred in 1 patient). If less than 25% of the items were missing, missing values were replaced by the average score of the non-missing items on that scale of that particular patient. Analyses were performed with the Statistical Package for the Social Sciences (SPSS) version 21.0.

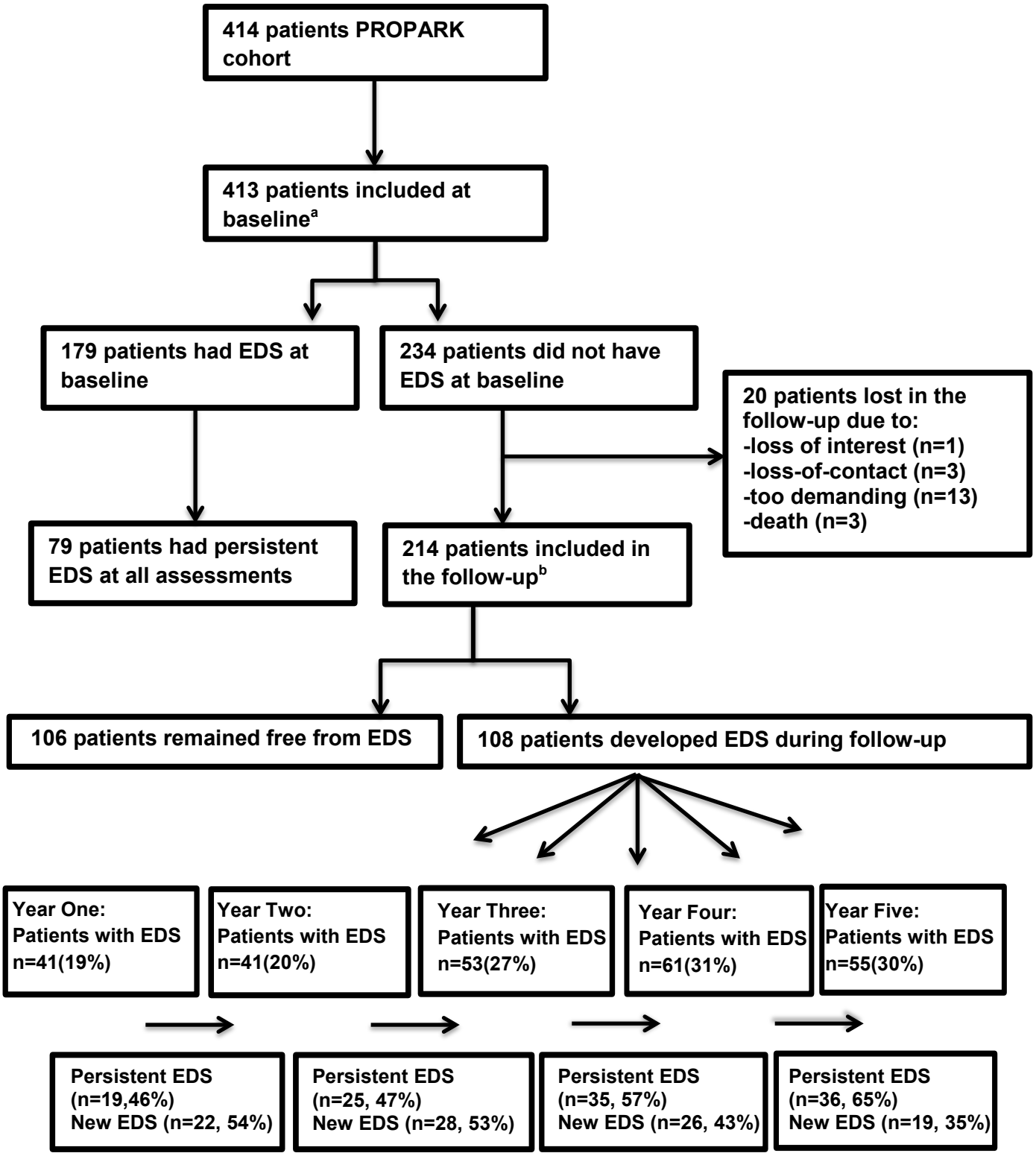
**RESULTS**

Of the 413 patients of whom an EDS score was available at baseline, 179 (43%) were classified as having EDS and 234 patients were classified as not having EDS (see for details Figure 4.1). Of the 234 patients without EDS at baseline, 108 patients (46%) developed this symptom during the follow-up period. During the 5-year follow-up period (Figure 4.1), EDS proved a non-persistent symptom, although the proportion of patients with EDS increased over time. In addition, with longer follow-up and disease duration, persistency of EDS increased: from 46% from year 1 to 2, to 65% from year 4 to 5.

*Variables associated with EDS at baseline (cross-sectional analysis)*

Patients with EDS at baseline were older, had a longer disease duration and higher Hoehn and Yahr stage, and performed worse with respect to motor function, activities of daily living and autonomic function (Table 4.1). A significant higher proportion of patients with EDS had a PIGD phenotype. They also presented with more severe cognitive impairment, depressive symptoms, nighttime sleep problems and more often suffered from hallucinations. Patients with EDS had a higher dopamine agonist and levodopa equivalent dose.

**Figure 4.1:** Flow Chart of follow-up for excessive daytime sleepiness




[a]*Data of these patients were used in the cross sectional analysis (objective 1) and the Linear Mixed Models (LMM) analysis (objective 2), n=413.*

[b]*Data of these patients were used in the survival analysis (objective 3), n=214.*

**Table 4.1:** Baseline data of patients with and without excessive daytime sleepiness (EDS)

| | Total | With EDS | Without EDS | p-values |
|---|---|---|---|---|
| N | 413 | 179 | 234 | |
| Age, yr | 61.14 (11.37) | 63.46 (10.47) | 59.37 (11.76) | <.001 |
| Sex, % male | 64.2 | 64.8 | 63.7 | .813[a] |
| DBS at baseline, % | 9.2 | 7.3 | 10.7 | .233[a] |
| Education, yr | 11.95 (4.11) | 11.74 (4.09) | 12.10 (4.13) | .377 |
| Age at onset, yr | 50.53 (11.89) | 51.26 (11.47) | 49.95 (12.22) | .266 |
| Disease duration, yr | 10.62 (6.53) | 12.20 (6.93) | 9.42 (5.96) | <.001 |
| Hoehn & Yahr, stage | 2 (2,3) | 3 (2,4) | 2 (2,3) | <.001[b] |
| SPES/SCOPA-Motor Impairment | 13.31 (4.90) | 14.82 (4.99) | 12.23 (4.55) | <.001 |
| SPES/SCOPA-Dyskinesia | 0.94 (1.62) | 0.98 (1.65) | 0.91 (1.60) | .635 |
| SPES/SCOPA-Motor Fluctuations | 0.78 (1.26) | 0.80 (1.22) | 0.77 (1.29) | .823 |
| SPES/SCOPA-ADL | 8.92 (3.56) | 10.26 (3.48) | 7.91 (3.29) | <.001 |
| PIGD dominant phenotype, % | 45.4 | 55.0 | 38.2 | .001[a] |
| BDI score | 10.21 (6.57) | 12.34 (6.72) | 8.57 (5.97) | <.001 |
| SCOPA-COG score[c] | 25.27 (6.68) | 23.31 (7.11) | 26.79 (5.92) | <.001 |
| MMSE score | 26.65 (2.82) | 25.98 (3.17) | 27.15 (2.41) | <.001 |
| SCOPA-SLEEP-NS score[d] | 4.51 (3.77) | 5.29 (3.80) | 3.92 (3.64) | <.001 |
| SCOPA-SLEEP-DS score[d] | 4.87 (3.73) | 8.39 (2.76) | 2.18 (1.43) | <.001 |
| SCOPA-AUT, total score[e] | 10.55 (5.71) | 12.87 (5.56) | 8.82 (5.20) | <.001 |
| SCOPA-AUT, GI score[e] | 2.72 (2.20) | 3.45 (2.26) | 2.16 (1.98) | <.001 |
| SCOPA-AUT, CV score[e] | 1.16 (1.19) | 1.42 (1.26) | 0.96 (1.10) | <.001 |
| SCOPA-AUT, UR score[e] | 6.72 (4.03) | 7.97 (4.08) | 5.77 (3.72) | <.001 |
| Hallucinations, % with | 16.9 | 25.1 | 10.6 | <.001 |
| Antidepressants, % with | 15.3 | 15.1 | 15.5 | .918[a] |
| Antihypertensives, % with | 20.8 | 24.6 | 17.9 | .100[a] |
| Benzodiazepine, % with | 22.3 | 24.0 | 21.0 | .470[a] |
| Total LDE, mg/day | 608 (463) | 729 (423) | 517 (473) | <.001 |
| LDE-Dopa, mg/day | 380 (375) | 454 (360) | 324 (377) | <.001 |
| LDE-DA dose, mg/day | 231 (226) | 275 (218) | 197 (227) | <.001 |

*Variables are expressed as means (standard deviations), except for gender (percentages), motor subtype (percentages) and Hoehn and Yahr stage (median ((interquartile range)). All differences are calculated with the independent-samples t-tests, except for*
*[a] Chi-square test and [b] Mann-Whitney U test.*
*[c] SCOPA-COG: cognitive function, higher scores reflect better functioning.*
*[d] SCOPA-SLEEP, NS score: nighttime sleep problems; DS score: daytime sleepiness*
*[e] SCOPA-AUT: sumscore autonomic functioning including items from the sections on gastrointestinal (GI), cardiovascular (CV) and urinary tract (UR).*
*Abbreviations: DBS, Deep Brain Surgery; ADL, activities of daily living; PIGD, postural instability gait difficulty; BDI, Beck depression inventory; MMSE, Mini-mental state examination; LDE, Levodopa dosage equivalent; DA, dopamine agonists.*

*Variables associated with longitudinal changes in EDS (LMM analysis)*

The assumptions for LMM were met and residuals from the LMM analysis were normally distributed. The final model of the LMM analysis showed that male gender, poorer nighttime sleep, presence of hallucinations, and cognitive and autonomic dysfunction at baseline were associated with higher EDS scores over time, whereas the motor impairment score was marginally significant (Table 4.2). In addition, less severe dyskinesias were also significantly related to higher EDS scores. The dose of DA agonists - but not the levodopa dose - and use of antihypertensive drugs were associated with higher EDS scores as well, whereas use of benzodiazepines was associated with lower EDS scores. There were no significant differences between the different classes of antihypertensive medication and the risk for the development of EDS (40% beta-antagonists vs 35% diuretics, p=0.63).

*Risk factors for future development of EDS (survival analysis)*

The multivariate Cox proportional hazards' model showed that a higher baseline EDS score, a PIGD phenotype, urinary tract symptoms and the use of antihypertensives were independent predictors of the future development of EDS in patients without this symptom at baseline (Table 4.3).

**Table 4.2:** Factors associated with higher SCOPA SLEEP DS scores over time in patients with PD

| | Unadjusted Model | | Adjusted Model | | Final Model | |
|---|---|---|---|---|---|---|
| | **B (95%CI)** | **p** | **B (95%CI)** | **p** | **B (95%CI)** | **p** |
| Age | 0.056 (0.041-0.072) | <.001[d] | 0.010 (-0.024-0.045) | .55 | 0.011 (-0.022-0.044) | .51 |
| Male gender | 0.540 (0.192-0.889) | .002[d] | 0.761 (0.055-1.466) | .04[d] | 0.781 (0.091-1.471) | .03[d] |
| Disease duration in years | 0.092 (0.066-0.117) | <.001[d] | 0.046 (-0.016-0.108) | .15 | 0.043 (-0.018-0.104) | .17 |
| SPES/SCOPA – Motor Impairment | 0.205 (0.167-0.242) | <.001[d] | 0.092 (-0.001-0.184) | .05 | 0.088 (-0.004-0.180) | .06 |
| SPES/SCOPA – ADL | 0.310 (0.262-0.358) | <.001[d] | 0.056 (-0.095-0.207) | .46 | 0.060 (-0.089-0.208) | .43 |
| SPES/SCOPA – Dyskinesia | 0.032 (-0.075-0.138) | .56 | -0.353 (-0.597- -0.109) | .005[d] | -0.394 (-0.632- -0.157) | .001[d] |
| SPES/SCOPA – Motor Fluctuations | 0.052 (-0.084-0.189) | .45 | -0.185 (-0.492-0.121) | .24 | | |
| PIGD dominant phenotype | 0.858 (0.515-1.201) | <.001[d] | -0.424 (-1.159 -0.310) | .26 | -0.392 (-1.118-0.333) | .29 |
| SCOPA-COG score[a] | -0.133(-0.160- -0.107) | <.001[d] | -0.090 (-0.150- -0.030) | .003[d] | -0.089(0.148- -0.029) | .004[d] |
| BDI score | 0.138 (0.113-0.164) | <.001[d] | 0.048 (-0.016-0.112) | .14 | 0.046 (-0.017-0.108) | .15 |
| Presence of hallucinations | 2.120 (1.653-2.588) | <.001[d] | 0.823 (-0.096-1.742) | .08 | 0.924 (0.026-1.823) | .04[d] |
| SCOPA-SLEEP-NS score[b] | 0.128 (0.084-0.172) | <.001[d] | 0.117 (0.016-0.217) | .02[d] | 0.109 (0.012-0.206) | .03[d] |
| SCOPA-AUT[c] GI score | 0.363 (0.287-0.439) | <.001[d] | 0.174 (0.002-0.347) | .05[d] | 0.179 (0.012-0.346) | .04[d] |
| SCOPA-AUT[c] CV score | 0.535 (0.390-0.679) | <.001[d] | 0.106 (-0.200-0.412) | .50 | 0.170 (-0.127-0.466) | .26 |
| SCOPA-AUT[c] UR score | 0.241 (0.199-0.284) | <.001[d] | 0.112 (0.019-0.206) | .02[d] | 0.108 (0.015-0.200) | .02[d] |
| Daily levodopa dose, p/100mg | 0.149 (0.103-0.196) | <.001[d] | 0.025 (-0.087-0.137) | .67 | 0.002 (-0.103-0.107) | .97 |
| Daily DA dose, p/100 mg | 0.264 (0.192-0.336) | <.001[d] | 0.348 (0.194-0.502) | <.001[d] | 0.336 (0.184-0.487) | <.001[d] |
| Use of anti-hypertensives | 0.803 (0.379-1.226) | <.001[d] | 1.241 (0.445-2.038) | .002[d] | 1.264 (0.475-2.053) | .002[d] |
| Use of benzodiazepines | -0.248 (-0.656-0.159) | .23 | -1.313 (-2.143- -0.484) | .002[d] | -1.444 (-2.246- -0.641) | <.001[d] |
| Use of antidepressants | 0.051 (-0.428-0.530) | .84 | -0.412 (-1.319-0.494) | .37 | | |

*Estimates are presented as B with 95% confidence intervals (CI), where a positive value is associated with a positive relationship between the baseline variable and SCOPA-SLEEP DS scores.*
*Abbreviations: ADL, activities of daily living; PIGD, postural instability gait difficulty; BDI, Beck depression inventory; DA, dopamine agonists.*
*[a] SCOPA-COG: cognitive function, higher scores reflect better functioning.*
*[b] SCOPA-SLEEP, NS score: nighttime sleep problems.*
*[c] SCOPA-AUT: sumscore autonomic functioning including items from the sections on gastrointestinal (GI), cardiovascular (CV) and urinary tract (UR).*
*[d] significant values*

**Table 4.3:** Longitudinal risk factor analysis for the development of excessive daytime sleepiness (EDS) in patients without EDS at baseline

| | Unadjusted Model | | Adjusted Model | | Final Model | |
|---|---|---|---|---|---|---|
| | **HR (95%CI)** | **p** | **HR (95%CI)** | **p** | **HR (95%CI)** | **p** |
| Age, p/yr increase | 1.012 (0.995-1.029) | .16 | 0.990 (0.963-1.017) | .47 | | |
| Gender, HR for males | 1.071 (0.718-1.596) | .74 | 1.265 (0.736-2.173) | .40 | | |
| Baseline EDS score, p/point increase | 1.367 (1.191-1.569) | <.001[d] | 1.400 (1.178-1.664) | <.001[d] | 1.361 (1.182-1.569) | <.001[d] |
| Disease duration, p/yr increase | 1.011 (0.981-1.042) | .47 | 0.984 (0.937-1.033) | .51 | | |
| SPES/SCOPA – Motor Impairment | 1.041 (0.996-1.088) | .07 | 1.003 (0.935-1.076) | .94 | | |
| SPES/SCOPA – ADL | 1.063 (1.003-1.125) | .04[d] | 1.012 (0.901-1.138) | .84 | 0.998 (0.934-1.066) | .95 |
| SPES/SCOPA – Dyskinesia | 1.000 (0.889-1.126) | .99 | 0.902 (0.746-1.091) | .29 | | |
| SPES/SCOPA – Motor Fluctuations | 1.017 (0.881-1.193) | .82 | 0.865 (0.660-1.133) | .29 | | |
| Motor phenotype, HR for PIGD dominant | 1.244 (0.998-1.550) | .07 | 1.882 (1.041-3.402) | .04[d] | 1.520 (1.003-2.303) | .05[d] |
| SCOPA-COG[a], p/point increase | 0.979 (0.945-1.014) | .24 | 1.012 (0.958-1.070) | .67 | | |
| BDI, p/point increase | 1.011 (0.980-1.043) | .50 | 1.016 (0.970-1.064) | .50 | | |
| Presence of hallucinations | 1.538 (0.859-2.752) | .15 | 0.818 (0.382-1.753) | .61 | | |
| SCOPA-SLEEP-NS[b], p/point increase | 1.005 (0.955-1.057) | .84 | 1.026 (0.949-1.108) | .52 | | |
| SCOPA-AUT[c], GI score p/point increase | 1.071 (0.973-1.178) | .16 | 1.035 (0.888-1.207) | .66 | | |
| SCOPA-AUT[c], CV score p/point increase | 1.145 (0.980-1.337) | .09 | 1.243 (0.970-1.594) | .09 | | |
| SCOPA-AUT[c], UR score p/point increase | 1.093 (1.041-1.147) | <.001[d] | 1.039 (0.960-1.125) | .34 | 1.070 (1.015-1.127) | .01[d] |
| Daily levodopa dose, p/100mg increase | 1.065 (1.014-1.117) | .01[d] | 1.077 (0.987-1.176) | .10 | 1.014 (0.959-1.073) | .61 |
| Daily DA dose, p/100 mg increase | 1.041 (0.962-1.127) | .32 | 1.048 (0.946-1.161) | .37 | | |
| Use of antihypertensives, | 1.780 (1.136-2.788) | .01[d] | 1.460 (0.835-2.551) | .18 | 1.624 (1.026-2.572) | .04[d] |
| Use of benzodiazepines | 0.701 (0.417-1.179) | .70 | 0.613 (0.297-1.263) | .18 | | |
| Use of antidepressants | 1.268 (0.763-2.107) | .36 | 1.207 (0.619-2.353) | .58 | | |

*All variables are expressed as hazard ratio (HR) with 95% confidence interval (CI).*
*Abbreviations: ADL, activities of daily living; PIGD, postural instability gait difficulty; BDI, Beck depression inventory; DA, dopamine agonists.*
*[a] SCOPA-COG: cognitive function, higher scores reflect better functioning.*
*[b] SCOPA-SLEEP, NS score: nighttime sleep problems.*
*[c] SCOPA-AUT: sumscore autonomic functioning including items from the sections on gastrointestinal (GI), cardiovascular (CV) and urinary tract (UR).*
*[d] significant values*

## DISCUSSION

We examined persistency, cross-sectional and longitudinal associations, and risk factors for EDS in a cohort of over 400 patients with PD who have been followed for up to five years. The analysis showed that EDS is not a stable feature but that its presence fluctuates. With longer follow-up, however, the proportion of patients with EDS increases and the feature becomes more persistent, indicating the relevance of evaluating its presence, particularly in patients who are at risk. We found that 69% of patients had EDS at some point during follow-up and that approximately 50% of patients who had no EDS at baseline reported this symptom at least once in the course of this study (Figure 4.1).

Our study is the largest longitudinal study on this subject so far.[4,5] The setup of our study is somewhat similar to a recent study conducted in a smaller population of de novo PD patients.[4] Interestingly, in spite of substantial differences between both studies concerning cohort composition, the results with respect to persistency, and identified associations and risk factors for EDS are remarkably similar. On account of this specific sampling strategy in our cohort, prevalence rates of EDS in our study are not representative of the population at large.

EDS in PD is assumed to be caused by the infestation of brain areas involved in the control of sleep and wakefulness.[18] In addition, dopaminergic treatment plays an important role as well, although the risk for EDS is significantly lower for levodopa compared to dopamine agonists, a finding that was replicated in our longitudinal analysis.

Previously reported variables that are associated with EDS and which emerged in our longitudinal analysis included male gender, dopamine agonist dosage, cognitive dysfunction, the presence of hallucinations, autonomic dysfunction, nighttime sleep problems, a higher baseline EDS score and a PIGD dominant motor phenotype. Age was only found associated with EDS in cross-sectional studies.[4,5]

Interestingly, the variables related to EDS that emerged from this study such as cognitive dysfunction, psychotic symptoms, autonomic dysfunction and PIGD were identified earlier as components of a coherent clinical predominant nondopaminergic (PND) symptom complex.[19] Notably, recent studies show that this symptom complex is prevalent early in the disease, and worsens with disease progression, which in turn plays an important role in characterizing subtypes of PD.[19,20] Hence, in accordance with the development and worsening of the aforementioned symptoms of nondopaminergic domains, the development of EDS likely is a consequence of progressive a-synuclein aggregate-related synaptopathy and axon degeneration of the central nervous system.[21] The correlation between EDS and the PND complex also raises the question whether the two could cancel each other out in the LMM analysis. After performing a more straightforward LMM analysis (only correcting for

age, disease duration and gender), the same variables were significant that were initially presented in Table 4.2. Another factor that is generally assumed to be associated with the occurrence of EDS in PD patients is an impaired nocturnal sleep.[22] Our results confirm this relationship. Additionally, we found that the use of night-time benzodiazepines was negatively associated with EDS severity, a finding corroborating with those of another study showing that PD patients treated with night-time clonazepam for nocturnal sleep disturbances, reported less EDS than those patients who were untreated.[22] In fact, post-hoc analysis showed that the nocturnal sleep disturbances and the use of night-time benzodiazepines shared the largest covariance with each other in the LMM. Both variables showed a large significant response when LMM analysis was only run with these two as variables. However, it must be noted that nocturnal sleep disturbances may not be the only responsible factor for EDS, since other studies did not confirm a relation between EDS and nocturnal sleep disturbances.[23]

In line with findings of a previous study, male gender emerged as a risk factor for EDS in our study.[4] Interestingly, such a relation has not yet been found in the general population, likely indicating a differential susceptibility for males with PD.[24]

In both our cross-sectional and longitudinal analysis, autonomic dysfunction was related with EDS, a finding in line with one prior cross-sectional study in de novo PD patients.[25] To date, no longitudinal study has yet been performed which included autonomic dysfunction as a baseline variable.[4,5] Since the autonomic system plays a critical role in regulating the function of numerous organs, we evaluated if particular autonomic sub-domains were responsible for the relation with EDS. This revealed that urinary tract symptoms showed the strongest association with EDS scores over time. The autonomic nervous system exerts its control through a broad central and peripheral network, which are both involved in PD and could contribute to the development of nocturia and subsequently nocturnal sleep disruption in this disorder.[3,26,27] This relation is supported by the beneficial effect of desmopressin acetate on nocturia in PD.[28]

Dyskinesias are common in advanced disease and associated with the prolonged use of levodopa.[29] In this study, less severe dyskinesias emerged as a risk factor for EDS. An earlier actigraphy study in PD found that patients with daytime sleepiness, measured by immobility, are more bradykinetic and less dyskinetic.[30]

Notably, dyskinesias did not emerge as a risk factor for EDS in the unadjusted LMM analysis. This likely indicates that when the analysis is controlled for differences in dopaminergic medication, the protective effect of increased daily motor activity on EDS, is absent. Although EDS score itself did not differ for PD patients with different age of onsets (AO<50: 4.76 ± 3.73 versus AO≥50:4.98 ± 3.74; p=0.56), one could still argue if EDS could be a heterogeneous phenomenon, where patients have different aetiologies for developing

EDS with different age of onsets. Interestingly, the daily dopamine agonists dosage was significantly higher in patients with an age of onset PD< 50, compared to those with an age of onset of ≥50 (AO< 50: 292 mg ± 237 mg versus AO≥50:169 mg ± 196 mg; p<0.001), whereas the latter had a lower SCOPA-COG score (AO<50: 27.62 ± 5.58 versus AO≥50: 22.89 ± 6.88; p<0.001). Therefore, in addition to multifactorial origin of EDS, there seems to be a significant role of dopamine agonists to the development of EDS in PD patients with a younger age of onset, whereas in those with an older age of onset cognitive decline seems to be the culprit.

Our study also revealed a new potentially modifiable risk factor for EDS in PD, namely the use of antihypertensives. In the general population sleepiness has been described as a common effect of antihypertensives and prevalence rates of 30-75% have been reported,[6] particularly with the use of beta-antagonists.[7] It is assumed that beta-antagonists exert this effect through their action on adrenergic receptors involved in the sleep-wake regulation. In our cohort, antihypertensive drugs were related to EDS, regardless of the class of antihypertensive drugs. If the effect of antihypertensive drugs is caused by the lowering of blood pressure, possibly in conjunction with dopaminergic medication on EDS in PD, then this should be further explored in future studies.

The finding that a clinical feature demonstrates a non-persistent behaviour over time yields important consequences for the interpretation of results derived from the LMM and the Cox Proportional Hazards model. In the LMM analyses, the data of all patients are used, whereas in the survival analysis only data of patients who are free of EDS at baseline are included. Although both procedures involve analysis of longitudinal data, they provide different answers to different questions, namely: “Which factors are associated with longitudinal changes in EDS? (LMM) ” versus “Which factors are associated with an increased risk of future EDS in patients who are free of this symptom at baseline? (Cox Proportional Hazards model)”

The strengths of this study are the prospective design, the broad clinical characterization, the limited loss to follow-up and the size of the cohort of patients with more advanced PD. Limitations involve the fact that certain baseline variables such as pain and sleep disordered breathing, which were earlier described as risk factors, were not included at baseline, and the fact that our cohort is hospital-based. The latter may have resulted in some over- or underestimation of certain associations, but it is unlikely that this has resulted in major distortions. In addition, our findings largely corroborated with those of an earlier population-based study on the novo PD patients.[4]

In conclusion, EDS is not a persistent phenomenon, although frequency and persistency increase with longer disease duration. Male gender, poorer nighttime sleep, cognitive and autonomic dysfunction, presence of hallucinations, less severe dyskinesias, higher dose of

dopamine agonists and use of antihypertensives were all associated with higher daytime sleepiness scores over time, whereas use of benzodiazepines was associated with lower scores. In addition, baseline SCOPA-SLEEP-DS scores and the PIGD motor phenotype were independent risk factors for the future development of EDS.

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Chapter 5:

# The course of insomnia in Parkinson's disease


Kangdi Zhu[1]; Jacobus J. van Hilten[1]; Johan Marinus[1]

[1]Department of Neurology, Leiden University Medical Center, Leiden, The Netherlands

Published in *Parkinsonism and Related Disorders* 2016;33:51-57

**ABSTRACT**

*Introduction.* Insomnia is a debilitating symptom in Parkinson's disease (PD) that has been scarcely investigated in a longitudinal design. Knowledge of factors associated with occurrence of insomnia may provide clues for an increased understanding of underlying pathophysiology and facilitate early detection. The objective of this study is to examine the course and factors associated with longitudinal changes in insomnia severity in patients with PD. *Methods.* Analyses were performed in data of the SCOPA-PROPARK cohort, a 5-year longitudinal cohort study (2003-2011) of 421 PD patients who have been examined annually. Linear mixed models were used to identify factors associated with longitudinal changes in scores of the SCOPA-SLEEP-Nighttime sleep (NS) problems section. A generalized estimating equations (GEE) analysis was performed to determine which baseline variables were associated with the different aspects of insomnia (sleep initiation or maintenance difficulty). *Results*. Baseline SCOPA-SLEEP-NS scores were available for 412 patients, of whom 110 (27%) had insomnia (i.e. score ≥7). Of the remaining 302 patients, 99 (33%) developed insomnia at some point during follow-up. More severe depressive symptoms, motor fluctuations, higher dopamine agonist doses and sleep medication use were independently associated with higher SCOPA-SLEEP-NS scores over time. GEE analysis did not identify an unique set of determinants that affected specific aspects of insomnia. *Conclusion.* The presence of depressive symptoms, motor fluctuations and the use of higher doses of dopamine agonists are associated with more severe insomnia. Attention to these aspects could potentially contribute to a better management of insomnia symptoms in PD.

## INTRODUCTION

Insomnia is a common sleep disorder in Parkinson's disease (PD) and affects up to 60% of patients according to earlier population-based prevalence studies.[1] The American Academy of Sleep Medicine defines insomnia as problems involving initiating sleep, maintaining sleep, early awakenings and poor overall sleep quality.[2] In PD, sleep fragmentation and early awakenings are the most common complaints, whereas initiation of sleep is often unimpaired.[3] Insomnia may be related to ageing, the progression of the disease or the use of drugs with a sleep-altering effect.[1-4] Insomnia has a great negative impact upon health-related quality of life[5,6] and is one of the most frequently reported non-motor symptoms in PD, with larger studies finding prevalence rates between 37 and 45%.[7,8] Remarkably, there are only a few longitudinal studies on insomnia in PD and information on its course and possible determinants is therefore scarce. To date only one large longitudinal study (n=231) has been performed,[1] which showed that insomnia often exhibits a fluctuating course and is associated with female gender, longer disease duration and coexistent depression. Cross-sectional studies on this topic showed that increased levels of anxiety and depression, impulsivity, excessive daytime sleepiness (EDS), fatigue, autonomic dysfunction and higher doses of dopaminergic medication are associated with insomnia in PD, whereas conflicting results emerged regarding disease severity.[3,4,9-12] However, cross-sectional studies provide limited information on the course and features that are longitudinally associated with insomnia. A thorough knowledge of factors that are associated with occurrence and severity of insomnia may provide clues for an enhanced understanding of the underlying pathophysiology, facilitate early detection and guide future intervention strategies. The aim of the current study was to use a prospective cohort design to determine the frequency, course, longitudinal associations and risk factors of insomnia in PD.

## METHODS

*Study design and participants*

Since 2013, post-hoc analyses on the PROPARK cohort have been performed to determine the longitudinal course of several non-motor domains.[13] The original purpose of the PROPARK cohort study was to evaluate the longitudinal course of several motor and non-motor symptoms in PD. The cohort included 421 PD patients who have been examined annually and followed for up to five years (i.e., six assessments) on several motor and non-motor features; this makes this study very well-suited for the purpose of identifying factors associated with longitudinal changes in insomnia in PD.[14] Patients were recruited from neurology clinics of university and regional hospitals in the western part of The Netherlands and all fulfilled the United Kingdom Parkinson's disease Society Brain Bank criteria for idiopathic PD.[15] The majority of patients were evaluated at the Leiden University Medical Centre, but more severely affected patients were offered the possibility to be examined at their homes to minimize selective drop-out. In view of the fact that we aimed to obtain information on the full spectrum of the disease, a recruitment strategy based on age-at-onset (< or ≥50 years) and disease duration (< or ≥10 years) was applied. We intended to recruit at least 100 patients in each of the four strata.[14] The medical ethical committee of the Leiden University Medical Centre approved the PROPARK study and written informed consent was obtained from all patients.[14]

*Assessment of baseline variables*

Baseline assessments were performed between 2003 and 2005. In the five subsequent annual visits, all patients received standardized assessments. The last assessments of individual patients were performed between 2008 and 2011. The assessments included an evaluation of demographic and clinical characteristics, family history of PD, and registration of antiparkinsonian medication. A levodopa dose equivalent (LDE) of daily levodopa and dopamine agonists dose was calculated for each patient at baseline. The total LDE is the sum of levodopa dosage equivalent (LDE-Dopa) and the dopamine agonist dosage equivalent (LDE-DA).[16] Diagnosis of PD and Hoehn & Yahr (H&Y) stages of the patients were ascertained at every assessment.[17] The following instruments were administered by qualified examiners: the SPES/SCOPA[18] (including sections on motor examination, activities of daily living and motor complications), the SCOPA-COG (cognitive function),[19] and the SCOPA-PC (psychiatric complications; items 1-5).[20] Over the years, there were in total five examiners, who all regularly attended retraining and recalibration sessions to prevent inter-rater variability. All patients were assessed during “on’’ and patients completed the following instruments themselves: the SCOPA-AUT (subscales gastrointestinal, urinary tract and cardiovascular),[21] the SCOPA-SLEEP (nighttime sleep problems [NS] and daytime

sleepiness [DS]),[22] and the Beck Depression Inventory (BDI).[23] For all instruments except the SCOPA-COG, higher scores reflect poorer functioning. Patients were classified according to motor subtype into those with and without postural-instability-and-gait difficulty (PIGD) by using a ratio of tremor score over PIGD score.[19] Patients with a ratio value <1.0 were classified as PIGD dominant, whereas those with values ≥1.0 were classified as non-PIGD dominant.[18,24]

*Ascertainment of insomnia*

Insomnia was assessed using the nighttime sleep (NS) section of the SCOPA-SLEEP questionnaire,[22] an instrument that was appraised as "recommended" by the Movement Disorder Society Sleep Scale Task Force (MDS-SSTF).[25] It consists of 5 items that evaluate problems with sleep initiation, sleep maintenance, early awakenings and subjective sleep quality. Patients were considered to suffer from insomnia if they scored ≥7.[22]

*Statistical analysis*

The objectives of the statistical analysis in this study were: 1) to examine which factors are associated with the presence of insomnia; 2) to evaluate which variables are associated with longitudinal variations in SCOPA-SLEEP-NS scores; and 3) to determine which specific aspects of insomnia are affected by the different baseline variables.

For objective 1 we evaluated which features were associated with insomnia in the baseline data of our population. Cross-sectional analyses were performed to assess differences at baseline between patients with and without insomnia using the appropriate tests.

For objective 2 a linear mixed models (LMM) analysis was performed using the data of all patients included in the follow-up. This method is suitable for identifying baseline variables that are associated with variation in SCOPA-SLEEP-NS scores over time. LMM takes into account that repeated measures in the same patient are correlated and a restricted maximum likelihood model with an autoregressive (heterogeneous) covariance structure type was used in all LMM analyses; this covariance structure takes into account that measurements performed closer in time are more strongly correlated than those that have been performed over longer intervals. Since heterogeneity between patients was expected in baseline levels and in change over time, random intercepts and slopes were used. Variables that have been found associated with insomnia in earlier studies were considered in the LMM. The H&Y stage was not included because it is partly determined by motor phenotype and the sumscore of motor impairment.

The relationship between variables that were associated with variation in SCOPA-SLEEP-NS scores over time were first analyzed including only one variable at a time (unadjusted model). Additionally, an adjusted model was performed that considered the main effects of

all significant baseline variables from the unadjusted model. The final model only included the variables that were significant from the adjusted model.
A generalized estimating equations (GEE) method was applied to determine if the same or different baseline variables determined the various characteristics of insomnia (i.e. the different items of the SCOPA-SLEEP-NS, e.g., difficulty initiating sleep, sleep maintenance or early awakenings) (objective 3). This method is suitable for identifying variables that are associated with variation in a binary outcome over time (here: the presence or absence of a particular insomnia symptom). Similar to the LMM procedure, an autoregressive (heterogeneous) covariance structure type was used. Scores on different items of each annual SCOPA-SLEEP-NS assessment were dichotomized, and patients were classified as impaired if they scored ≥1 on a specific item. Baseline variables that are significant from the unadjusted model were entered in the multivariate analysis. All analyses were performed with the Statistical Package for the Social Sciences (SPSS) version 21.0.

**RESULTS**

Of the 412 patients of whom a baseline SCOPA-SLEEP-NS score was available, 110 (27%) were classified as having insomnia at baseline (Figure 5.1). Of the remaining 302 patients who did not have insomnia at baseline, 99 (37%) developed this symptom in one or more of the subsequent assessments. Overall, 51% of the patients had insomnia at some point during follow-up, either at baseline or during follow-up. Insomnia was not a persistent symptom (Figure 5.1), although persistency increased with longer follow-up (33-46%). There was no trend towards an increase in insomnia over time at a group level (Supplement 5.1 Figure S5.1a). We also found that in comparison with patients without insomnia at baseline, patients with insomnia at baseline consistently had higher scores during the follow-up period, although a clear tendency towards lower scores can be observed over the course of follow-up, probably due to regression to the mean (Supplement 5.1 Figure S5.1b). Higher insomnia scores during follow-up were also found for patients with depression (BDI≥15) at baseline and patients classified as PIGD phenotype at baseline (Supplement 5.1 Figure S5.1c and S5.1d).

*Variables associated with insomnia at baseline (cross-sectional analysis)*

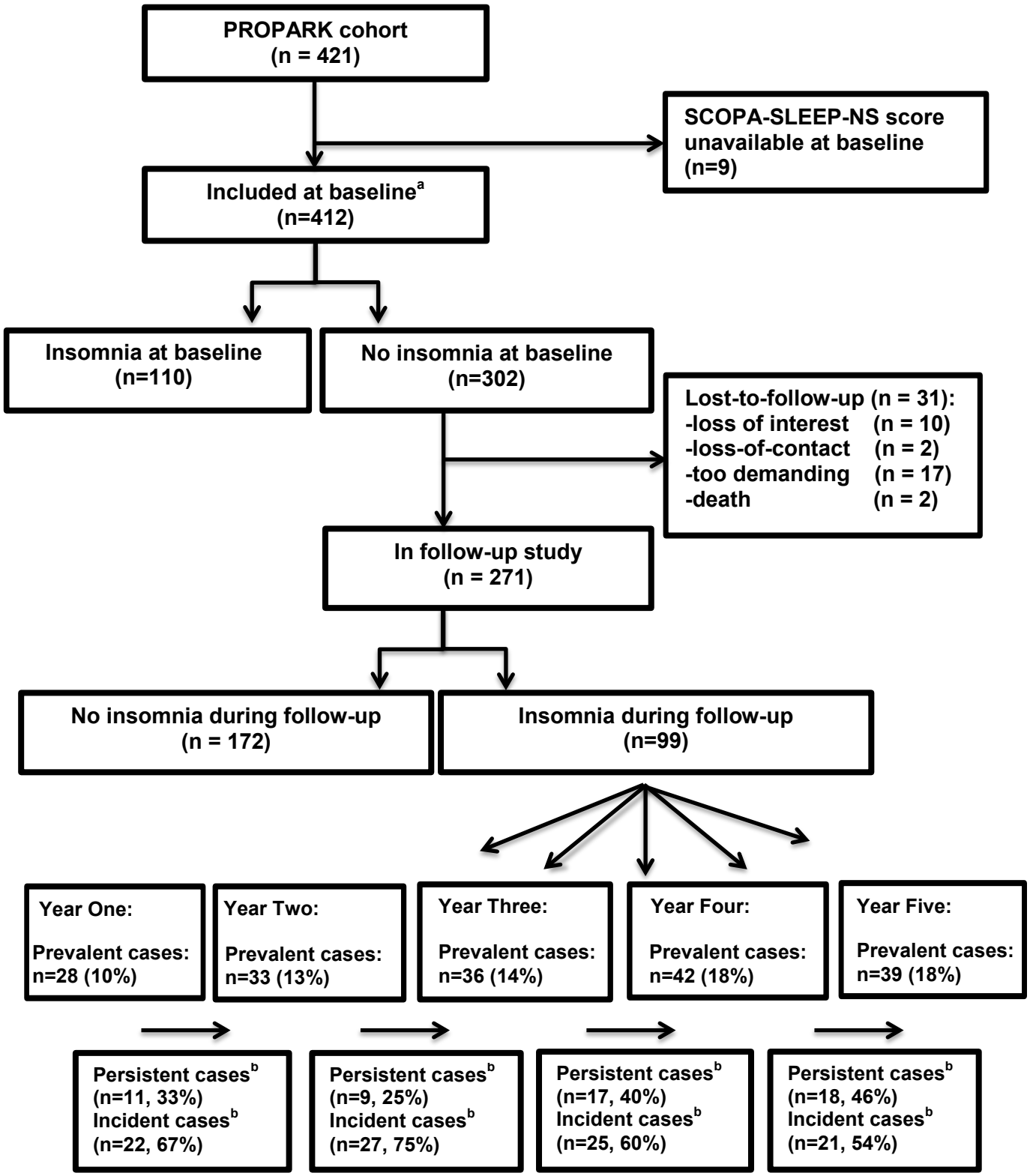
A larger proportion of patients with insomnia at baseline were female. In addition, patients with insomnia at baseline had a longer disease duration, higher H&Y stage, and higher levels of disability and autonomic dysfunction (Table 5.1). Patients with insomnia also had more severe motor complications (dyskinesias and motor fluctuations), depressive symptoms and EDS. They suffered more often from hallucinations and presented more often

with a PIGD phenotype. Regarding the use of medication, insomnia patients used more sleep medication and higher doses of antiparkinsonian medication.

*Variables associated with longitudinal changes in SCOPA-SLEEP-NS score (LMM analysis)*
The final model of the LMM analysis showed that higher BDI scores and more severe motor fluctuations at baseline were associated with higher SCOPA-SLEEP-NS scores over time (Table 5.2). Regarding medication, higher dopamine agonist doses and sleep medication use were also significantly related to higher SCOPA-SLEEP-NS scores.

*Variables associated with specific characteristics of insomnia (GEE analysis)*
The final model of the GEE analysis showed that depressive symptoms and motor fluctuations were associated with all items of insomnia (items 1-5, Table 5.3). Urinary tract symptoms only affected items 2, 3 and 5 (frequent awakenings, lying awake too long and subjective lack of sleep), cardiovascular symptoms affected items 1 and 3 (sleep initiation and lying awake too long), while female gender and EDS both only contributed to item 4 (early awakenings) and item 5 (subjective lack of sleep quality), respectively.
Regarding medication, items 2, 4 and 5 (frequent and early awakenings, subjective lack of sleep) were all associated with higher dopamine agonists doses, while items 1, 2 and 4 (sleep initiation, frequent and early awakenings) were associated with sleep medication use.
To verify the robustness of our findings, we repeated the analysis at a cut-off level of ≥2 (Supplement 5.1 Table 5.1). Again we found no specific set of variables that was uniquely associated with a particular aspect of insomnia. The BDI score was still associated with all aspects of insomnia, while at this cut-off the severity of motor fluctuations was associated with 3 aspects (instead of 5 at the lower cut-off), and use of sleep medication with 4 aspects (instead of 3 at the lower cut-off). Some disagreement was to be expected due to potential misclassification of certain patients.

**Figure 5.1:** Flow Chart of follow-up for insomnia




*[a] Data of these patients were used in the cross sectional analysis (objective 1), the Linear Mixed Models (LMM) analysis (objective 2) and the Generalized Estimating Equations (GEE) analysis (objective 3), n=412.*

*[b] Percentages of persistent insomnia for a particular year were calculated by dividing the number of patients with insomnia who also had insomnia in the previous year by the total number of patients with insomnia in that particular year. For example in year 2, a total number of 33 patents were classified as having insomnia, of which 11 also had been classified as having insomnia in year 1, resulting in a percentage of 33 (i.e. 11/33). So in other words, if a patient had insomnia in year one and year two, the patient counts as a case of persistent insomnia in year two. If a patient did not have insomnia in year one, but had insomnia in year two and three, he or she counted as a case of persistent insomnia in year three.*

**Table 5.1:** Baseline data of patients with and without insomnia

| | Total | With insomnia | Without insomnia | p-values |
|---|---|---|---|---|
| N | 412 | 110 | 302 | |
| Age, yr | 61.1 (11.4) | 61.0 (11.1) | 61.2 (11.6) | .88 |
| Sex, % female | 35.8 | 44.7 | 31.2 | .007[a,†] |
| Time of follow-up, yr | 4.56 (1.13) | 4.82 (0.81) | 4.47 (1.22) | |
| Sleep medication, % | 16.8 | 35.5 | 10.0 | <0.001[a,f] |
| Education, yr | 12.0 (4.1) | 12.1 (4.2) | 11.9 (4.1) | .54 |
| Disease duration, yr | 10.6 (6.5) | 12.0 (6.3) | 9.9 (6.6) | .002[f] |
| Age at onset, yr | 50.5 (11.9) | 49.1 (11.4) | 51.3 (12.1) | .08 |
| Hoehn & Yahr, stage | 2 (2,3) | 3 (2,4) | 2 (2,3) | .02[b,†] |
| SPES/SCOPA Motor Impairments | 13.3 (4.9) | 13.8 (4.7) | 13.1 (5.0) | .23 |
| SPES/SCOPA Dyskinesias | 0.9 (1.6) | 1.4 (1.9) | 0.7 (1.4) | .006[b,†] |
| SPES/SCOPA Motor Fluctuations | 0.8 (1.3) | 1.4 (1.5) | 0.6 (1.1) | <.001[b,f] |
| SPES/SCOPA ADL | 8.9 (3.6) | 9.7 (3.5) | 8.6 (3.5) | .006[f] |
| Motor phenotype, PIGD dominant, % | 45.2 | 53.8 | 42.1 | .04[a,f] |
| Beck Depression Inventory | 10.2 (6.6) | 13.7 (7.3) | 8.4 (5.3) | <.001[†] |
| SCOPA-COG[c] | 25.3 (6.7) | 25.2 (6.7) | 25.3 (6.7) | .79 |
| SCOPA-SLEEP, NS[d] | 4.5 (3.8) | 9.7 (2.1) | 2.6 (2.1) | <.001[†] |
| SCOPA-SLEEP, EDS[d] | 4.9 (3.7) | 5.6 (4.2) | 4.5 (3.4) | .005[f] |
| SCOPA-AUT, GI score[e] | 2.7 (2.2) | 3.3 (2.3) | 2.4 (2.1) | <.001[f] |
| SCOPA-AUT, UR score[e] | 6.7 (4.0) | 7.8 (3.9) | 6.2 (4.0) | <.001[f] |
| SCOPA-AUT, CV score[e] | 1.2 (1.2) | 1.6 (1.4) | 1.0 (1.0) | <.001[†] |
| Hallucinations, % with | 16.9 | 23.1 | 13.8 | .02[a,f] |
| Total LDE, mg/day | 608 (463) | 735 (449) | 545 (458) | <.001[†] |
| LDE-Dopa, mg/day | 379 (375) | 471 (377) | 334 (366) | <.001[f] |
| LDE-DA dose, mg/day | 231 (226) | 263 (227) | 214 (224) | .04[f] |

*Variables are expressed as means (standard deviations), except for gender (percentages), motor subtype (percentages), Hoehn and Yahr stage (median ((interquartile range)). All differences are calculated with the independent-samples t-tests, except for*
*[a] Chi-square test and [b] Mann-Whitney U test.*
*[c] SCOPA-COG: cognitive function, higher scores reflect better functioning.*
*[d] SCOPA-SLEEP, NS score: nighttime sleep, insomnia DS score: daytime sleepiness*
*[e] SCOPA-AUT: sumscore autonomic functioning including items from the sections on gastrointestinal (GI), cardiovascular (CV) and urinary tract (UR).*
*[f] Significant variables*

*Abbreviations: ADL, activities of daily living; PIGD, postural instability gait difficulty; LDE, Levodopa dosage equivalent; DA, dopamine agonists.*

**Table 5.2:** Factors associated with higher SCOPA-SLEEP NS scores over time

| | Unadjusted Model[a] | | Adjusted Model[b] | | Final Model[c] | |
|---|---|---|---|---|---|---|
| **Variable** | **B (95%CI)** | **P** | **B (95%CI)** | **P** | **B (95%CI)** | **P** |
| Age | 0.01 (-0.04-0.01) | .40 | | | | |
| Female gender | 0.45 (-1.04-0.14) | .13 | | | | |
| Disease duration, yr | 0.06 (0.01-0.10) | .009[g] | -0.03 (-0.08-0.02) | .26 | | |
| SPES/SCOPA – Motor Impairment | 0.01 (-0.05-0.07) | .78 | | | | |
| SPES/SCOPA – ADL | 0.13 (0.05-0.21) | .002[g] | -0.09 (-0.19-0.02) | .10 | | |
| SPES/SCOPA – Dyskinesia | 0.12 (-0.05-0.30) | .17 | | | | |
| SPES/SCOPA – Motor Fluctuations | 0.65 (0.43-0.88) | <.001[g] | 0.45 (0.19-0.70) | .001[g] | 0.41 (0.19-0.63) | <.001[g] |
| PIGD dominant phenotype | 0.72 (0.12-1.32) | .002[g] | -0.25 (-0.86-0.37) | .44 | | |
| SCOPA-COG score[d] | 0.01 (-0.05-0.04) | .80 | | | | |
| Presence of hallucinations | 0.73 (-0.04-1.50) | .06 | | | | |
| SCOPA-SLEEP-DS score[e] | 0.15 (0.07-0.22) | <.001[g] | 0.09 (0.01-0.17) | .04[g] | 0.07 (-0.01-0.14) | .07 |
| BDI score | 0.20 (0.16-0.24) | <.001[g] | 0.16 (0.11-0.21) | <.001[g] | 0.16 (0.11-0.20) | <.001[g] |
| SCOPA-AUT[f] GI score | 0.16 (0.03-0.29) | .02[g] | -0.10 (-0.24-0.05) | .18 | | |
| SCOPA-AUT[f] CV score | 0.47 (0.23-0.71) | <.001[g] | 0.19 (-0.06-0.45) | .14 | | |
| SCOPA-AUT[f] UR score | 0.16 (0.09-0.23) | <.001[g] | 0.07 (-0.01-0.15) | .07 | | |
| Daily levodopa dose, p/100mg | 0.11 (0.03-0.18) | .007[g] | 0.03 (-0.06-0.12) | .49 | | |
| Daily DA dose, p/100 mg | 0.22 (0.10-0.35) | <.001[g] | 0.17 (0.04-0.30) | .01[g] | 0.13 (0.01-0.25) | .03[g] |
| Use of sleep medication | 2.33 (1.60-3.05) | <.001[g] | 1.63 (0.87-2.39) | <.001[g] | 1.59 (0.89-2.30) | <.001[g] |

*Estimates are presented as B with 95% confidence intervals (CI), where a positive value is associated with a positive relationship between the baseline variable and SCOPA-SLEEP NS scores.*
*Abbreviations: ADL, activities of daily living; PIGD, postural instability gait difficulty; BDI, Beck depression inventory; DA, dopamine agonists.*
[a] *The unadjusted model between NSP scores and the baseline variables were analyzed including one covariate at a time.*
[b] *The adjusted model includes only the significant variables (p<.05) from the unadjusted model.*
[c] *The final model includes only the significant variables (p<.05) from the adjusted model.*
[d] *SCOPA-COG: cognitive function, higher scores reflect better functioning.*
[e] *SCOPA-SLEEP, DS: daytime sleepiness.*
[f] *SCOPA-AUT: sumscore autonomic functioning including items from the sections on gastrointestinal (GI), cardiovascular (CV) and urinary tract (UR).*
[g] *significant values*

**Table 5.3:** Variables associated with specific aspects of insomnia (GEE analysis)

| Domain/Factor | OR | 95% CI | P |
|---|---|---|---|
| 1.Difficulty falling asleep | | | |
| SPES/SCOPA – Motor Fluctuations | 1.15 | 1.00-1.32 | .05 |
| BDI score | 1.03 | 1.00-1.06 | .03 |
| Use of sleep medication | 1.97 | 1.21-3.20 | .006 |
| SCOPA-AUT – Cardiovascular | 1.23 | 1.04-1.45 | .01 |
| 2.Been awake too often | | | |
| SPES/SCOPA – Motor Fluctuations | 1.36 | 1.11-1.67 | .004 |
| BDI score | 1.07 | 1.03-1.11 | .001 |
| Use of sleep medication | 1.88 | 1.08-3.29 | .03 |
| Daily DA dose, p/100 mg | 1.14 | 1.04-1.25 | .004 |
| SCOPA-AUT – Urinary Tract | 1.09 | 1.04-1.10 | .001 |
| 3. Lying awake too long | | | |
| SPES/SCOPA – Motor Fluctuations | 1.31 | 1.10-1.57 | .003 |
| BDI score | 1.07 | 1.03-1.11 | <.001 |
| SCOPA-AUT – Urinary Tract | 1.07 | 1.02-1.12 | .008 |
| SCOPA-AUT – Cardiovascular | 1.23 | 1.04-1.46 | .02 |
| 4. Waking too early | | | |
| SPES/SCOPA – Motor Fluctuations | 1.20 | 1.03-1.40 | .02 |
| BDI score | 1.05 | 1.01-1.09 | .007 |
| Use of sleep medication | 1.76 | 1.06-2.93 | .03 |
| Daily DA dose, p/100 mg | 1.13 | 1.05-1.23 | .002 |
| Female Gender | 1.55 | 1.09-2.22 | .03 |
| 5. Had too little sleep | | | |
| SPES/SCOPA – Motor Fluctuations | 1.20 | 1.02-1.21 | .03 |
| BDI score | 1.07 | 1.03-1.12 | <.001 |
| SCOPA-SLEEP-DS score[a] | 1.08 | 1.03-1.14 | .003 |
| Daily DA dose, p/100 mg | 1.12 | 1.03-1.23 | .009 |
| SCOPA-AUT – Urinary Tract | 1.08 | 1.02-1.13 | .007 |

*For every aspect of insomnia (i.e., items in the SCOPA-SLEEP-NS) only variables are reported that were independently and significantly associated with changes in that aspect over time. All variables are expressed as odds ratio (OR) with 95% confidence interval (CI) , where a value >1 indicates that a higher score of that variable is associated with a higher risk to develop that specific aspect of insomnia.*

*Abbreviations: BDI, Beck depression inventory; DA, dopamine agonists.*
[a] *SCOPA-SLEEP, DS: daytime sleepiness.*

## DISCUSSION

In this study we examined cross-sectional and longitudinal associations of insomnia in a hospital-based cohort of 421 PD patients who have been followed over a mean follow-up time of 4.56 years. Our study is the largest longitudinal study on this subject so far. Of the patients enrolled in the study, 51% had insomnia at some point, and 37% of those who did not have insomnia at baseline developed this symptom during follow-up. These rates are comparatively lower than those of an earlier population-based longitudinal study,[1] which may be due to differences in study settings (population-based versus hospital-based) and population characteristics (more female patients in the Norwegian study [50.1 versus 35.8%]). In addition, this study used a different questionnaire with different response options, and although similar aspects of insomnia were evaluated, broader criteria for insomnia were applied: i.e., patients were classified as having insomnia if they reported sleeping problems during the night or used sleeping pills due to sleeping problems and had experienced these symptoms for at least 1 month, while our patients were only classified as having insomnia if the applied cut-off score was attained.

With longer follow-up, the proportion of patients with insomnia increased slightly and insomnia became more persistent, indicating the importance of monitoring this symptom, particularly in patients who are at risk.

Among patients with PD, insomnia is a frequent symptom and past studies reported a significant reduction of total sleep time even in untreated PD patients with mild disease, as compared to healthy age-matched controls.[26] The causes of insomnia in PD are multifactorial, including the underlying degeneration of sleep regulatory centers, comorbidity, or the sleep-altering effect of antiparkinsonian drugs.[1,3,4] In addition, neuropsychiatric symptoms, nocturia, dyskinesias, pain or dystonia[27] as well as intrinsic circadian rhythm dysregulation[28] could significantly contribute to sleep disruption in PD patients.

Our cross-sectional analysis showed that, similar to the findings of another longitudinal study,[1] insomnia was associated with longer disease duration and occurred more often in females.

The analysis of changes in overall insomnia severity over time (i.e. with the SCOPA-SLEEP-NS score as dependent variable) confirmed that depressive symptoms and the dosage of dopamine agonists - variables that had previously been identified only in cross-sectional studies[4,5] - were associated with higher scores over time. Previous studies in PD showed that insomnia and depression frequently co-exist.[1,3,5,7] It is important to realize that insomnia is a characteristic of depression, and that therefore the two features are inherently related.[29] In one study in PD, insomnia remained related to depressive symptoms, even when subjects who qualified for the criteria of depression were excluded.[3] Hitherto, the direction of the relation between insomnia and depression has remained a chicken and egg dilemma

because of the cross-sectional design of most previous studies.[3,5,7] Our results suggest that depressive symptoms precede insomnia in PD, and consistently more severe insomnia was reported during follow-up by patients with more depressive symptoms at baseline. This indicates that adequate management of depression may not only improve the patient's mood, but the possibility exists that this also has an ameliorating effect on insomnia. However, it must be noted that the reverse relationship is also found in PD, as we observed in an earlier study.[30] We can therefore safely conclude that there is a bi-directional longitudinal relationship between the two symptoms, i.e. depressive symptoms may precede insomnia, whereas insomnia symptoms may in turn contribute to the development of depression in PD.

The finding that higher dopamine agonist doses are associated with insomnia in PD is in line with an earlier study.[4] However, this issue is controversial and it must be noted that while certain dopamine agonists may worsen insomnia, others have shown to improve sleep quality in PD.[31] In addition, timing of dopamine agonists is also an important aspect in treating insomnia.[4] Dopamine agonists could have an impact on sleep in PD in different ways. Firstly, treatment with dopaminergic therapy increases the patients risk to develop hallucinations, which in turn could cause nocturnal sleep disturbances.[7] This is supported by the finding that patients with insomnia and hallucinations at baseline also had higher dopamine agonist doses than those with insomnia, but without hallucinations (mean (SD) dopamine agonists dosage (p/100mg) of 3.88 (2.45) vs 2.36 (1.97), p=0.001). Secondly, dopamine plays an important role in sleep-wake regulation.[4] Further, dopamine agonists have biphasic effects on sleep-wakefulness and this effect has been attributed to D2 receptor stimulation; at low doses they reduce wakefulness and enhance sleep, whereas high doses induce opposite effects.[31]

We found that a higher levodopa dose was associated with more insomnia in the unadjusted – but not the adjusted - LMM analysis (Table 5.2). This indicates that the presence of other variables may confound this association and may in part explain the contradictory results observed in some previous studies, with some reporting a positive[32,33] and others reporting a negative[34] association. Lastly, motor fluctuations were found associated with more severe insomnia symptoms over time and this complication of levodopa treatment usually increases in prevalence and severity as PD progresses. Several effective strategies to target motor fluctuations are now available[35] and these approaches may potentially have a beneficial influence on insomnia in PD.

Because the various aspects of insomnia may be differentially affected by PD – for example, sleep initiation is usually preserved whereas sleep maintenance is typically affected -, we evaluated if different sets of variables were associated with the separate insomnia items. These analyses revealed that, in line with our results from the LMM, more severe depressive

symptoms and motor fluctuations were longitudinally associated with all aspects of insomnia; although the odds ratios for motor fluctuations are higher, one should bear in mind that the metrics of the two scales are different: the SPES/SCOPA – Motor Fluctuations subscale has a range from 0-6, where the BDI has a range from 0-63. A higher dose of dopamine agonists was found to be associated with early and frequent awakenings and subjective lack of sleep, but not with sleep initiation or lying awake too long. This implies that dopamine agonists selectively affect sleep maintenance and not sleep initiation. Interestingly, urinary tract symptoms were associated with three out of five items (frequent awakenings, lying awake too long and subjective lack of sleep) and cardiovascular symptoms with two (sleep initiation and lying awake too long), even though both symptoms did not emerge as significant findings in our overall LMM analysis. In addition, our cross-sectional analysis also showed that patients with insomnia reported more urinary tract symptoms at baseline. Therefore, these patients could, for instance, benefit from desmopressin acetate, which may reduce the number of voidings at night and consequently disrupt nocturnal sleep less frequently.[36] Various (pharmacological and non-pharmacological) strategies to manage nocturia exist. [36] For more resistant forms of nocturia, a referral to an urologist for additional evaluation might be necessary.[37] The relation between cardiovascular symptoms and insomnia is less straightforward; however, there are indications that involvement of the vagal system -, which is an essential part of the cardiac autonomic network - and the locus coeruleus are affected in the course of the disease.[38] Interestingly, the locus coeruleus also plays a role in sleep/wake regulation, and damage to this structure could therefore contribute to sleep disruption in PD patients.[39] Findings of one earlier study suggested that sleep disturbances and cardiac autonomic dysfunction might together be a marker for disease severity in PD.[40] Collectively, the findings suggest that involvement of both anatomical structures may play a role in the development of sleep disturbances in PD. EDS only contributed to the item subjective lack of sleep, which is to be expected since frequent falling asleep during the day could contribute to less sleep at night and therefore a subjective lack of sleep.

Collectively our GEE analysis does not provide clues for an unique set of determinants for specific aspects of insomnia, but does give more insight that certain variables may play a pertinent role in particular aspects of insomnia.

At baseline, 69 patients used sleep medication, of whom 56 (81%) were on benzodiazepines. Since we had no information on the efficacy of drugs used to treat insomnia (e.g. benzodiazepines), we evaluated if the use of these drugs confounded the presence of insomnia. This seemed not to be the case since patients on medication for sleep disorders had significantly higher SCOPA-SLEEP-NS scores than patients without sleep medication (mean (SD) score: 7.25 (4.13) vs 3.96 (3.45), $p<0.001$) and sleep medication demonstrated a positive relationship in the LMM and the GEE. These results may suggest

that the potential effect of sleeping drugs on insomnia is limited, rendering a confounding influence on the results unlikely (i.e. under- rather than overestimation).

The strengths of this study are the prospective design, the broad clinical characterization, the limited loss to follow-up and the size of the cohort. Limitations involve the fact that certain patient-specific baseline variables, such as fatigue, sleep-disordered breathing and symptoms of impulse-control disorder, which have been reported as risk factors,[8,9] were not included. Another point worth considering is that our cohort is hospital-based and this may have resulted in some over- or underestimation of certain associations, but it seems unlikely that this has resulted in significant distortions of our conclusions. Finally, assessments were performed on an annual basis, while the time frame of the SCOPA-SLEEP-NS concerns the past month, which may not be fully representative of the entire past year.

In conclusion, insomnia is an important problem in PD, occurring in more than half of patients with this disorder. The presence of depressive symptoms, motor fluctuations and the use of higher doses of dopamine agonists are associated with more severe insomnia. Attention to these aspects could potentially contribute to a better management of insomnia symptoms in PD.

**SUPPLEMENT 5.1**

**Figure S5.1**: Course of mean SCOPA-SLEEP-NS scores for patients included at baseline (N=412)

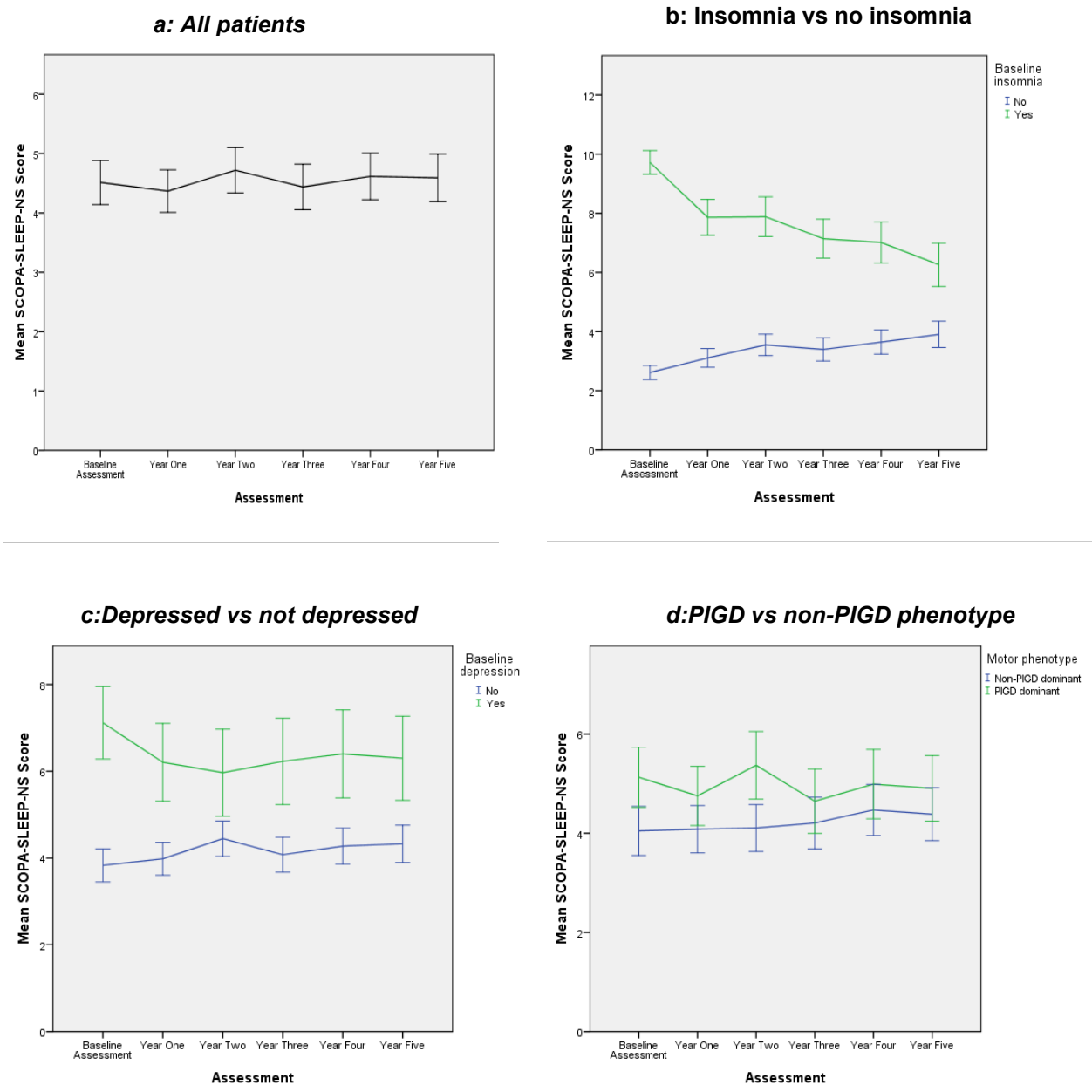



***Figure 1a***: *Mean SCOPA-SLEEP-NS score over time for all patients included at baseline.*
***Figure 1b***: *Mean SCOPA-SLEEP-NS scores over time for patients with insomnia (SCOPA-SLEEP-NS≥7)vs no insomnia at baseline.*
***Figure 1c***: *Mean SCOPA-SLEEP-NS scores over time for depressed (BDI≥15) vs non- depressed patients at baseline*
***Figure 1d***: *Mean SCOPA-SLEEP-NS scores over time for patients with PIGD-dominant vs non-PIGD-dominant motor phenotype*

*Error bars are displayed as +/- 2SE (95%CI)*
*Abbreviations: PIGD: postural-instability-and-gait difficulty*

**Table S5.1:** Variables associated with specific aspects of insomnia (GEE analysis; cutoff ≥2)

| Domain/Factor | OR | 95% CI | P |
|---|---|---|---|
| 1.Difficulty falling asleep | | | |
| BDI score | 1.06 | 1.02-1.09 | <.001 |
| Use of sleep medication | 3.33 | 1.97-5.63 | <.001 |
| SPES/SCOPA – Motor Fluctuations | 1.02 | 0.76-1.37 | .91 |
| 2.Been awake too often | | | |
| SPES/SCOPA – Motor Fluctuations | 1.22 | 1.05-1.42 | .009 |
| BDI score | 1.07 | 1.04-1.10 | <.001 |
| Use of sleep medication | 1.78 | 1.12-2.83 | .02 |
| Daily DA dose, p/100 mg | 1.13 | 1.04-1.21 | .002 |
| SCOPA-AUT – Urinary Tract | 1.05 | 1.00-1.10 | .04 |
| SCOPA-SLEEP-DS score[a] | 1.06 | 1.01-1.11 | .02 |
| 3. Lying awake too long | | | |
| SPES/SCOPA – Motor Fluctuations | 1.17 | 1.00-1.36 | .05 |
| BDI score | 1.06 | 1.03-1.09 | <.001 |
| Use of sleep medication | 2.06 | 1.28-3.31 | .003 |
| SCOPA-SLEEP-DS score[a] | 1.05 | 1.00-1.11 | .05 |
| 4. Waking too early | | | |
| SPES/SCOPA – Motor Fluctuations | 1.18 | 1.00-1.38 | .05 |
| BDI score | 1.11 | 1.07-1.15 | <.001 |
| Use of sleep medication | 1.69 | 1.09-2.62 | .02 |
| Daily DA dose, p/100 mg | 1.11 | 1.02-1.20 | .01 |
| 5. Had too little sleep | | | |
| SPES/SCOPA – Motor Fluctuations | 1.10 | 0.95-1.27 | .23 |
| BDI score | 1.09 | 1.06-1.13 | <.001 |
| Daily DA dose, p/100 mg | 1.09 | 1.00-1.18 | .05 |
| SCOPA-SLEEP-DS score[a] | 1.06 | 1.00-1.12 | .05 |

*For every aspect of insomnia (i.e., items in the SCOPA-SLEEP-NS) only variables are reported that were independently and significantly associated with changes in that aspect over time.*
*A patient is classified as impaired on a certain aspect, if a score of ≥2 is obtained.*
*All variables are expressed as odds ratio (OR) with 95% confidence interval (CI) , where a value >1 indicates that a higher score of that variable is associated with a higher risk to develop that specific aspect of insomnia.*
*Abbreviations: BDI, Beck depression inventory; DA, dopamine agonists.*
[a] *SCOPA-SLEEP, DS: daytime sleepiness.*

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# Chapter 6:

## Associated and predictive factors of depressive symptoms in patients with Parkinson's disease


Kangdi Zhu[1]; Jacobus J. van Hilten[1]; Johan Marinus[1]

[1]Department of Neurology, Leiden University Medical Center, Leiden, The Netherlands

Published in *Journal of Neurology* 2016;263:1215-1225

**ABSTRACT**

Depression is one of the most common non-motor symptoms in Parkinson's disease (PD). A thorough understanding of factors associated with depressive symptomatology may facilitate early detection and guide future intervention strategies. The objective of the study was to determine associated and predictive factors of depression in patients with PD. Analyses were performed in data of the SCOPA-PROPARK cohort, a 5-year hospital-based longitudinal cohort of over 400 PD patients who have been examined annually. Linear mixed models using data of all patients were used to identify factors associated with longitudinal changes in Beck Depression Inventory (BDI) scores. A survival analysis using data of patients without depression at baseline was performed to identify risk factors for future depression (i.e. BDI ≥ 15). The proportion of patients with depression was approximately 20% and remained stable during follow-up, with approximately half of cases showing a persistent course. Female gender, more severe disability, more severe motor fluctuations, autonomic and cognitive dysfunction, poorer nighttime sleep and daytime sleepiness were independently associated with higher BDI scores over time. Higher baseline BDI score, daytime sleepiness and a higher levodopa dosage were risk factors for future depression. Depression is common in PD, where it may follow a persistent or non-persistent course. Apart from motor fluctuations and levodopa dose, depressive symptoms in PD are mainly associated with factors of non-dopaminergic origin. This suggests that depression in PD is an inherent consequence of the progressive pathobiology of the disease, which may render its treatment with currently available treatment options difficult.

## INTRODUCTION

With a prevalence of about 40%, depression is one of the most common non-motor symptoms of Parkinson's disease (PD).[1] It contributes significantly to the disease burden[2] and several studies identified depression as the main determinant of poor quality of life in PD patients.[3] Symptoms that contribute to the clinical semiology of depression show an overlap with those primarily related to PD or those related to the side effects associated with the use of medication.[4] This renders the identification of depression in PD difficult and it is assumed that this condition frequently remains unrecognized.[5] Increased knowledge of associated and risk factors of depression in PD may therefore facilitate its early detection, provide insight into the nature of this condition, and guide future intervention strategies.[5,6]

In earlier studies in PD, consistent relations have been found between depression and age, anxiety, insomnia and dementia. However, contradictory findings have been reported for the relation between depression and gender, disease stage, levodopa treatment and motor subtype [postural instability/gait difficulty (PIGD)].[7-20]

These inconsistencies are likely explained by differences between studies concerning sample size, population characteristics and study design. Most previous studies on depression in PD had a cross-sectional design and, to our knowledge, only three longitudinal studies have been performed to date.[7,10,11] One longitudinal, hospital-based study (n = 685) showed that longer disease duration, greater disability, and a positive family history of motor neuron disease were risk factors associated with the development of depression.[10] Another hospital-based study (n = 184) found that the severity of depression in PD varied over time, with groups showing a remittent (35%), stable (34%) or progressive (31%) form.[7] The largest longitudinal, population-based case–control study performed by Becker et al. (3637 PD patients and controls) showed an almost twofold increased risk to develop depression in the patients with PD. Female gender and long-term levodopa usage emerged as the most important risk factors of depression.[11] Unfortunately, in all longitudinal studies the number of baseline features used in the analysis was limited. This specifically pertains to non-dopaminergic features, which are less sensitive to dopaminergic medication and may provide a more complete and accurate evaluation of disease severity and progression in PD.[21]

The PROPARK cohort study includes over 400 PD patients who have been examined annually and followed for 5 years (i.e., six assessments) on a broad range of motor and non-motor features.[22] This cohort is therefore very well-suited to investigate which factors are associated with: (1) the presence of depression in PD; (2) the longitudinal changes in severity of depressive symptoms; and (3) the development of future depression in PD.

## METHODS

*Study design and participants*

Patients were recruited from neurology clinics of university and regional hospitals in the western part of The Netherlands and all fulfilled the United Kingdom Parkinson's disease Society Brain Bank criteria for idiopathic PD.[23] The majority of patients were evaluated at the Leiden University Medical Center, but more severely affected patients were offered the possibility to be examined at their homes to prevent selective dropout. In view of the fact that we aimed to obtain information on the full spectrum of the disease, a recruitment strategy based on age at onset (< or ≥50 years) and disease duration (< or ≥10 years) was applied. We intended to recruit at least 100 patients in each of the four strata.[22] The medical ethical committee of the Leiden University Medical Center approved the PROPARK study and written informed consent was obtained from all patients.[22]

*Assessment of baseline variables*

At baseline (2003–2005) and the five subsequent annual visits all patients received standardized assessments. The assessments included an evaluation of demographic and clinical characteristics, family history of PD, and registration of antiparkinsonian medication. A levodopa dose equivalent (LDE) of daily levodopa and dopamine agonists dose was calculated for each patient at baseline. The total LDE is the sum of levodopa dosage equivalent (LDE-Dopa) and the dopamine agonist dosage equivalent (LDE-DA).[24] Diagnosis and Hoehn & Yahr (H&Y) stages of the patients were ascertained at every assessment.[25] The following instruments were administered by qualified examiners: the SPES/SCOPA[26] (including sections on motor examination, activities of daily living and motor complications), the SCOPA-COG cognitive function,[27] and the SCOPA-PC (psychotic symptoms; items 1–5).[28] Over the years, there were in total five examiners, who all regularly attended retraining and recalibration sessions to prevent inter-rater variability. All patients who used dopaminergic medication were assessed during "on''. Patients completed the following instruments themselves: the SCOPA-AUT (three autonomic domains: gastrointestinal, urinary tract and cardiovascular),[29] the SCOPA-SLEEP [with sections on nighttime sleep problems (NS) and daytime sleepiness (DS)],[30] and the Beck Depression Inventory (BDI).[31] For all instruments except the SCOPA-COG, higher scores reflect poorer functioning. Patients were classified according to motor subtype using a ratio of tremor score (SPES/SCOPA)[26] over PIGD score (SPES/SCOPA).[27] A total tremor or PIGD score of 0 was replaced by 0.5. Patients with a ratio value <1.0 were classified as PIGD dominant, whereas those with values from ≥1.0 were classified as non-PIGD dominant.[32]

*Ascertainment of depression*

Depression was assessed using the Beck Depression Inventory (BDI),[31] a valid and reliable instrument that includes 21 items with four response options (0–3). In accordance with the results of an earlier study,[33] a PD patient was classified as depressed if a BDI score of 15 or higher was attained.

*Statistical analysis*

Given objective 1 we first evaluated which features were associated with the presence of depression in the baseline data of our population. Cross-sectional analyses were performed to assess differences at baseline between patients with and without depression. Chi square tests were used for comparing categorical variables, while independent t-tests were used for comparing normally distributed continuous variables; the Mann–Whitney U test was used if continuous variables were not normally distributed.

For objective 2 a linear mixed models (LMM) analysis was performed using the data of all patients included in the follow-up. This method allows for the identification of baseline variables that are associated with variation in BDI scores over time. LMM take into account that repeated measures in the same subject are not independent but correlated. An advantage of this method is that it can deal with missing data in the outcome, and therefore this analysis does not have to be restricted to patients with a complete follow-up. A restricted maximum likelihood (REML) model with an autoregressive (heterogeneous) covariance structure type was used in all LMM analyses; this assumes that measurements that are closer in time are more strongly correlated than those that are further apart. Since heterogeneity between patients was expected in baseline levels and in change over time, random intercepts and random slopes were used. Baseline variables that have been found associated with depression in earlier studies were considered in the LMM. These included: age, gender, sumscore of motor impairment and activities of daily living (SPES/SCOPA), motor phenotype, presence of hallucinations (score ≥1 on item 1 of the SCOPA-PC), autonomic dysfunction score (gastrointestinal, urinary tract and cardiovascular domains), sumscore for nighttime sleep problems, sumscore of cognitive dysfunction (SCOPA-COG), dosage of antiparkinsonian medication (LDE-Dopa, LDE-DA) and the use of antidepressants.

The Hoehn and Yahr stage was not included because it is partly determined by motor phenotype and the sumscore of motor impairment and disease duration was excluded because it is partly determined by age. Anxiety scores were not taken into account in the analyses because of the strong and intricate relation with depression;[34] its inclusion could therefore have obscured the relation with other characteristics.

A few other baseline variables were added because a relation with development of depression could be presumed. These included: sumscore for daytime sleepiness, sumscore of dyskinesias and the sumscore of motor fluctuations. The relationship between variables that are associated with variation in BDI scores over time was first analyzed including only one variable at a time (unadjusted model). Additionally, an adjusted model was performed that considers the main effects of all significant baseline variables from the unadjusted model. The final model only includes the variables that were significant from the adjusted model.

For objective 3 we performed a survival analysis in the data of patients who had no depression at baseline with the same variables that were considered in the LMM, while also the baseline BDI score was added in this analysis. Survival time was calculated as the difference in years between the dates on which depression was first reported and the date of the patient's baseline assessment. Patients were considered to have an event ('uncensored') if they scored ≥15 on the BDI. If a patient did not have an event during the complete follow-up, he or she was 'withdrawn alive' and classified as 'censored'. In case a patient had missed 1 year and had no depression in the previous and following year, we assumed that the patient had not developed depression in that year. For the survival analysis, we first performed univariate analyses to evaluate which baseline variables were associated with future development of depression (unadjusted model). An adjusted model was performed to take the potential influence of confounders into account. The final model only includes the variables that were significant from the adjusted model and were simultaneously entered in a multivariate Cox proportional hazards' model.

Given the potential influence of antidepressant use of on depression status, a secondary analysis was performed in which patients were classified as depressed (i.e. had an 'event') if they attained a score ≥15 on the BDI or used antidepressants.

Risk factors for the development of depression were calculated as hazard ratios (HR) with 95% confidence intervals (CI), with a HR >1 indicating that the particular baseline variable is associated with a higher risk of developing depression.

Analyses were performed with the Statistical Package for the Social Sciences (SPSS) version 21.0.

## RESULTS

Of the 411 patients of whom a baseline BDI score was available, 87 (21%) were classified as depressed and 324 patients were classified as non-depressed (see for details Figure 6.1). Of the 324 patients who did not have depression at baseline, 90 patients (28%) developed this symptom during the follow-up period. The proportion of patients with depression remained relatively stable during follow-up (from 21% at baseline to 20% in year 5). During the 5-year follow-up period the presence of depression among patients varied considerably, with approximately half of cases showing a persistent course (Figure 6.2).

*Variables associated with depression at baseline (cross-sectional analysis)*

Patients with depression at baseline were older, had a longer disease duration and higher Hoehn and Yahr stage, and performed worse with respect to motor function, activities of daily living, motor fluctuations and dyskinesias (Table 6.1). A significant higher proportion of patients with depression had a PIGD phenotype. They also had significantly more cognitive impairment, daytime sleepiness, nighttime sleep problems and autonomic dysfunction, and more often suffered from hallucinations. No significant differences were found regarding the use of antidepressive or antiparkinsonian medication for depressed patients as compared to non-depressed patients.

*Variables associated with longitudinal changes in BDI (LMM analysis)*

The final model of the LMM analysis showed that female gender, more difficulties with activities of daily living and motor fluctuations, more cognitive impairment, more nighttime sleep problems and increased daytime sleepiness at baseline were associated with higher BDI scores over time (Table 6.2). In addition, autonomic dysfunction (urinary and cardiovascular domains) and the use of antidepressive medication were significantly related to higher BDI scores.

**Figure 6.1**: Flowchart of follow-up for depression

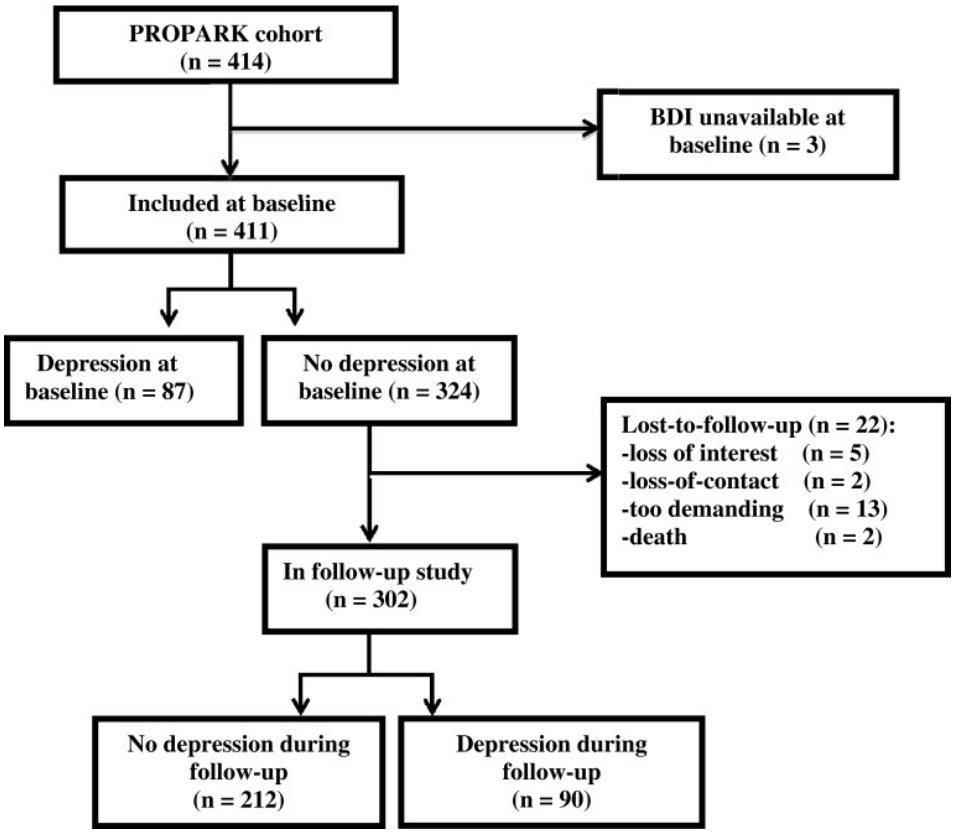
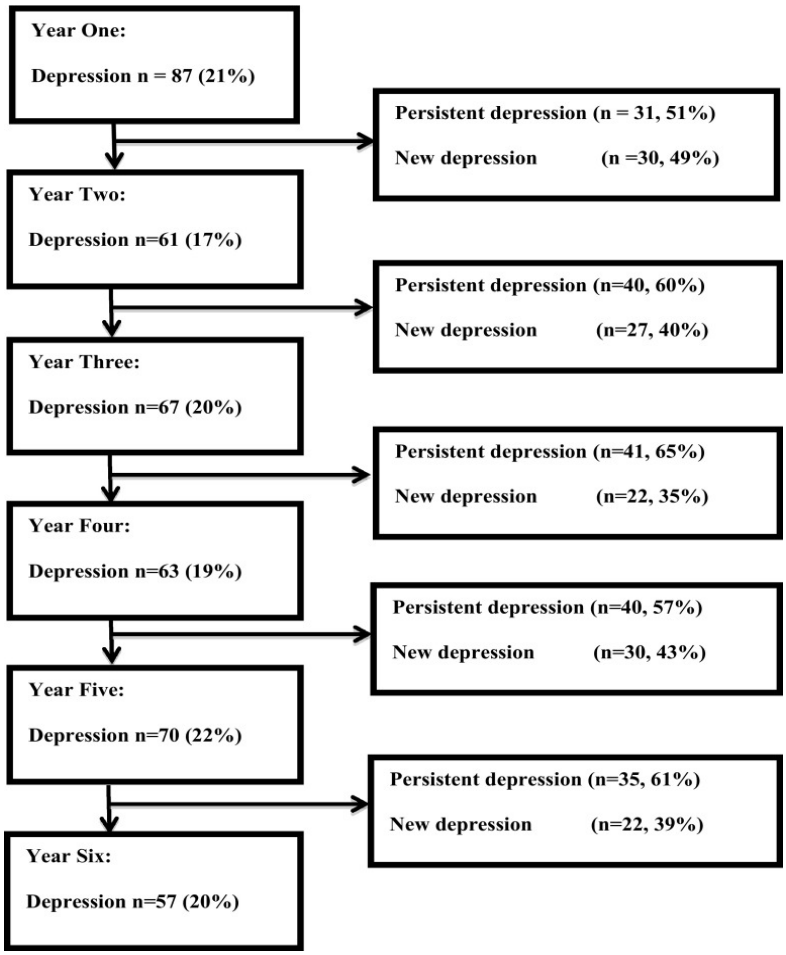


**Figure 6.2**: Flowchart of entire baseline population for the occurrence and persistence of depression.




*Percentages of persistent depression for a particular year were calculated by dividing the number of patients with persistent depression by the total number of depressed patients in the subsequent year. For instance, a total number of 61 patents were classified as depressed in year 2, of which 31 also had been classified as depressed in the previous year, resulting in a percentage of 51 (i.e., 31/61)*

**Table 6.1:** Baseline data of patients with and without depression

| | Total | With depression | Without depression | p-values |
|---|---|---|---|---|
| N | 411 | 87 | 324 | |
| Age, yr | 61.07 (11.38) | 63.65 (12.49) | 60.38 (10.97) | .02[f] |
| Sex, % female | 35.5 | 42.5 | 33.6 | .12[a] |
| Antidepressants, % | 15.4 | 19.5 | 14.2 | .22 |
| Education, yr | 11.97 (4.11) | 11.47 (4.49) | 12.10 (4.00) | .20 |
| Disease duration, yr | 10.64 (6.55) | 12.00 (6.67) | 10.28 (6.47) | .03[f] |
| Age at onset, yr | 50.43 (11.87) | 51.66 (11.98) | 50.11 (11.84) | .28 |
| Hoehn & Yahr, stage | 2 (2,3) | 3 (2,4) | 2 (2,3) | <.001[b,f] |
| SPES/SCOPA Motor Impairments | 13.31 (4.90) | 15.48 (5.30) | 12.71 (4.59) | <.001[f] |
| SPES/SCOPA Dyskinesias | 0.94 (1.62) | 1.41 (1.82) | 0.81 (1.54) | .006[f] |
| SPES/SCOPA Motor Fluctuations | 0.78 (1.26) | 1.19 (1.57) | 0.67 (1.14) | .006[f] |
| SPES/SCOPA ADL | 8.92 (3.56) | 10.86 (3.93) | 8.40 (3.28) | <.001[f] |
| Motor phenotype, PIGD dominant, % | 45.1 | 71.1 | 38.2 | <.001[a,f] |
| Beck Depression Inventory | 10.21 (6.57) | 20.06 (5.86) | 7.57 (3.54) | <.001[f] |
| SCOPA-COG[c] | 25.32 (6.67) | 22.13 (7.54) | 26.18 (6.15) | <.001[f] |
| SCOPA-SLEEP, NS[d] | 4.52 (3.77) | 7.12 (3.87) | 3.83 (3.44) | <.001[f] |
| SCOPA-SLEEP, EDS[d] | 4.88 (3.74) | 6.14 (3.83) | 4.54 (3.64) | <.001[f] |
| SCOPA-AUT, GI score[e] | 2.72 (2.20) | 3.79 (2.31) | 2.43 (2.08) | <.001[f] |
| SCOPA-AUT, UR score[e] | 6.72 (4.03) | 8.46 (4.46) | 6.28 (3.79) | <.001[f] |
| SCOPA-AUT, CV score[e] | 1.16 (1.19) | 1.83 (1.37) | 0.98 (1.08) | <.001[f] |
| Hallucinations, % with | 17.0 | 30.0 | 13.7 | .001[a,f] |
| Total LDE, mg/day | 609 (464) | 670 (423) | 593 (474) | .17 |
| LDE-Dopa, mg/day | 380 (375) | 441 (363) | 363 (378) | .09 |
| LDE-DA dose, mg/day | 232 (226) | 229 (218) | 232 (229) | .90 |

*Variables are expressed as means (standard deviations), except for gender (percentages), motor subtype (percentages) and Hoehn and Yahr stage (median ((interquartile range)). All differences are calculated with the independent-samples t-tests, except for*
*[a] Chi-square test and [b] Mann-Whitney U test.*
*[c] SCOPA-COG: cognitive function, higher scores reflect better functioning.*
*[d] SCOPA-SLEEP, NS score: nighttime sleep problems; DS score: daytime sleepiness*
*[e] SCOPA-AUT: sumscore autonomic functioning including items from the sections on gastrointestinal (GI), cardiovascular (CV) and urinary tract (UR).*
*[f] Significant values*
*Abbreviations: DBS, Deep Brain Surgery; ADL, activities of daily living; PIGD, postural instability gait difficulty; BDI, Beck depression inventory; LDE, Levodopa dosage equivalent; DA, dopamine agonists.*

**Table 6.2:** Factors associated with higher BDI scores over time in patients with PD

| | Unadjusted Model[a] | | Adjusted Model[b] | | Final Model[c] | |
|---|---|---|---|---|---|---|
| **Variable** | **B (95%CI)** | **P** | **B (95%CI)** | **P** | **B (95%CI)** | **P** |
| Age | 0.10 (0.07-0.12) | <.001[g] | -0.01 (-0.03-0.03) | .85 | | |
| Female gender | 1.62 (1.04 -2.21) | <.001[g] | 1.08 (0.49 -1.67) | <.001[g] | 0.96 (0.44-1.48) | <.001[g] |
| SPES/SCOPA – Motor Impairment | 0.33 (0.26-0.39) | <.001[g] | 0.05 (-0.03 -0.12) | .25 | | |
| SPES/SCOPA – ADL | 0.63 (0.55-0.70) | <.001[g] | 0.14 (0.01-0.26) | .04[g] | 0.16 (0.07-0.25) | <.001[g] |
| SPES/SCOPA – Dyskinesia | 0.67 (0.50-0.85) | <.001[g] | -0.12 (-0.33--0.09) | .25 | | |
| SPES/SCOPA – Motor Fluctuations | 1.20 (0.97-1.42) | <.001[g] | 0.30 (0.06-0.54) | .02[g] | 0.35 (0.14-0.56) | .001[g] |
| PIGD dominant phenotype | 2.71 (2.14-3.28) | <.001[g] | 0.13 (-0.48-0.74) | .68 | | |
| SCOPA-COG score[d] | -0.30 (-0.34--0.26) | <.001[g] | -0.20 (-0.25--0.15) | <.001[g] | -0.19 (-0.23--0.14) | <.001[g] |
| Presence of hallucinations | 3.60 (2.83-4.36) | <.001[g] | 0.25 (-0.55-1.05) | .54 | | |
| SCOPA-SLEEP-NS score[e] | 0.53 (0.46-0.60) | <.001[g] | 0.43 (0.35-0.50) | <.001[g] | 0.47 (0.40-0.54) | <.001[g] |
| SCOPA-SLEEP-DS score[e] | 0.51 (0.37-0.66) | <.001[g] | 0.23 (0.15-0.31) | <.001[g] | 0.25 (0.18-0.32) | <.001[g] |
| SCOPA-AUT[f] GI score | 0.85 (0.73-0.98) | <.001[g] | 0.28 (0.14-0.43) | <.001[g] | 0.10 (-0.03-0.23) | .13 |
| SCOPA-AUT[f] CV score | 1.61 (1.37-1.84) | <.001[g] | 0.45 (0.19-0.72) | .001[g] | 0.36 (0.13-0.60) | .002[g] |
| SCOPA-AUT[f] UR score | 0.57 (0.50-0.64) | <.001[g] | 0.13 (0.04-0.21) | .003[g] | 0.18 (0.11-0.25) | <.001[g] |
| Daily levodopa dose, p/100mg | 0.40 (0.32-0.48) | <.001[g] | -0.04 (-0.13-0.06) | .44 | | |
| Daily DA dose, p/100 mg | 0.12 (-0.14-0.37) | .37 | | | | |
| Use of antidepressants | 2.82 (2.01-3.62) | <.001[g] | 1.52 (0.75-2.30) | <.001[g] | 1.55 (0.86-2.24) | <.001[g] |

*Estimates are presented as B with 95% confidence intervals (CI), where a positive value is associated with a positive relationship between the baseline variable and BDI scores.*
*Abbreviations: ADL, activities of daily living; PIGD, postural instability gait difficulty; BDI, Beck depression inventory; DA, dopamine agonists.*
[a] *The unadjusted model between BDI scores and the baseline variables were analysed including one covariate at a time.*
[b] *The adjusted model includes only the significant variables (p<.05) from the unadjusted model.*
[c] *The final model includes only the significant variables (p<.05) from the adjusted model.*
[d] *SCOPA-COG: cognitive function, higher scores reflect better functioning.*
[e] *SCOPA-SLEEP, DS: daytime sleepiness NS: Nighttime sleep problems*
[f] *SCOPA-AUT: sumscore autonomic functioning including items from the sections on gastrointestinal (GI), cardiovascular (CV) and urinary tract (UR).*
[g] *significant values*

*Variables associated with persistent depression*

Of the total of 354 patients of whom at least three measurements were available, 152 were classified as depressed either at baseline or during one of the follow-up assessments (Fig. 2). Of these 152 patients, 58 patients had a persistent form of depression (i.e. >50% of assessments qualifying for depression) and 94 patients had a non-persistent form (≤50% of assessments qualifying for depression).

For patients with a persistent form of depression, the median (interquartile range) number of episodes of depression was 4 (3, 5), whereas for patients with a non-persistent form the median was 1 (1, 2). In comparison with baseline values of patients with non-persistent depression, patients with persistent depression were older, more often female, longer diseased, and also had more severe motor impairments (SPES-Motor and H&Y) and cognitive impairment (Supplement 6.1 Table S6.1). In addition, at baseline these patients already exhibited more severe depressive symptoms and were more often treated with antidepressants.

*Risk factors for future development of depression (survival analysis)*

The multivariate Cox proportional hazards' model showed that a higher baseline BDI score, daytime sleepiness and a higher levodopa dosage were independent predictors for future development of depression in patients who were non-depressed at baseline (Table 6.3).

For the secondary analysis, also patients using antidepressive medication were classified as depressed, which resulted in an increase of patients classified as depressed at baseline and an inherent decrease of the population at risk for future development of depression. In this scenario 89 patients out of a total of 272 developed depression during follow-up; 21 of those 89 patients were classified as depressed solely because of antidepressant use. The same three variables (higher baseline BDI score, increased daytime sleepiness and a higher levodopa dosage) emerged from the multivariate Cox proportional hazards' model.

**Table 6.3:** Longitudinal risk factor analysis of the development of depression in patients without depression at baseline

| | Unadjusted Model[a] | | Adjusted Model[b] | | Final Model[c] | |
|---|---|---|---|---|---|---|
| | **HR (95%CI)** | **P** | **HR (95%CI)** | **P** | **HR(95%CI)** | **P** |
| Age, p/yr increase | 1.03 (1.01-1.05) | .007[g] | 1.01 (0.98-1.04) | .45 | | |
| Gender, HR for females | 1.09 (0.71-1.67) | .70 | | | | |
| Baseline BDI score, p/point increase | 1.31 (1.23-1.40) | <.001[g] | 1.29 (1.19-1.40) | <.001[g] | 1.27 (1.18-1.36) | <.001[g] |
| Disease duration, p/yr increase | 1.01 (0.98-1.05) | .38 | | | | |
| SPES/SCOPA – Motor Impairments | 1.04 (0.98-1.09) | .18 | | | | |
| SPES/SCOPA – ADL | 1.11 (1.04-1.18) | .001[g] | 0.98 (0.91-1.06) | .64 | | |
| SPES/SCOPA – Dyskinesia | 1.12 (0.99-1.27) | .07 | | | | |
| SPES/SCOPA – Motor Fluctuations | 1.24 (1.06-1.46) | .008[g] | 0.92 (0.75-1.13) | .42 | | |
| Motor phenotype, HR for PIGD dominant | 1.56 (1.02-2.38) | .04[g] | 0.90 (0.54-1.50) | .69 | | |
| SCOPA-COG[d], p/point increase | 0.95 (0.92-0.98) | .002[g] | 0.97 (0.93-1.01) | .18 | | |
| Presence of hallucinations, yes/no | 2.11 (1.23-3.64) | .007[g] | 1.42 (0.78-2.59) | .26 | | |
| SCOPA-SLEEP-DS[e], p/point increase | 1.16 (1.10-1.22) | <.001[g] | 1.11 (1.05-1.18) | .001[g] | 1.10 (1.04-1.17) | .001[g] |
| SCOPA-SLEEP-NS[e], p/point increase | 1.09 (1.03-1.15) | .002[g] | 0.99 (0.92-1.06) | .68 | | |
| SCOPA-AUT, GI[f] score p/point increase | 1.01 (1.00-1.21) | .05[g] | 0.92 (0.82-1.03) | .16 | | |
| SCOPA-AUT, CV[f] score p/point increase | 1.33 (1.13-1.34) | .001[g] | 1.10 (0.89-1.35) | .38 | | |
| SCOPA-AUT, UR[f] score p/point increase | 1.09 (1.03-1.14) | .002[g] | 0.98 (0.91-1.05) | .60 | | |
| Daily levodopa dose, p/100mg increase | 1.12 (1.07-1.18) | <.001[g] | 1.12 (1.03-1.21) | .006[g] | 1.09 (1.03-1.15) | .004[g] |
| Daily DA dose, p/100 mg increase | 1.12 (1.03-1.21) | .007[g] | 1.08 (0.97-1.20) | .15 | | |
| Use of antidepressants, yes/no | 1.51 (0.87-2.63) | .15 | | | | |

*All variables are expressed as hazard ratio (HR) with 95% confidence interval (CI).*
*Abbreviations: ADL, activities of daily living; PIGD, postural instability gait difficulty; BDI, Beck depression inventory; DA, dopamine agonists.*
*[a] The unadjusted model between BDI scores and the baseline variables were analyzed including one covariate at a time.*
*[b] The adjusted model includes only the significant variables (p<.05) from the unadjusted model.*
*[c] The final model includes only the significant variables (p<.05) from the adjusted model.*
*[d] SCOPA-COG: cognitive function, higher scores reflect better functioning.*
*[e] SCOPA-SLEEP, DS score: daytime sleepiness NS: Nighttime sleep problems*
*[f] SCOPA-AUT: sumscore autonomic functioning including items from the sections on gastrointestinal (GI), cardiovascular (CV) and urinary tract (UR).*
*[g] significant values*

## DISCUSSION

Depression in PD likely results from complex interactions among genetic vulnerabilities, cognitive predisposition, age-associated neurobiological changes and stressful events. Although deficiencies in the dopaminergic, serotonergic and cholinergic networks have all been suggested to play a role in the pathobiology of depression in PD,[35,36] the multisystem nature of the disease renders it difficult to pinpoint the specific causes of depression in this condition. Against this background, knowledge of associated and risk factors of depression may provide insight into the nature of depression in PD.

In this study, we examined the presence and course of depression over 5 years in a large cohort of over 400 patients with PD. The prevalence of depression during follow-up was stable, at approximately 20%, which corresponds with findings of another longitudinal hospital-based study.[10] We further found that depression may persist or show a non-persistent course, which corroborates with findings of the study by Rojo et al.[7] Compared to patients with a non-persistent course, patients with persistent depression were older, more often female and longer diseased. Interestingly, these patients had more severe depressive symptomatology at baseline, even though they were more often treated with antidepressants. Our findings further suggest that patients with persistent depression suffer more advanced PD.

One might wonder if PD patients with persistent depression (n = 58) differed in progression on other non-motor and motor domains as compared to patients who were persistently non-depressed (n = 202). After performing an additional analysis in which we adjusted for differences in age, gender and disease duration, we found that persistent depression was associated with worse performance over time on all domains. (Supplement 6.2 Table S6.2).

*"Which factors are associated with longitudinal changes in depressive symptoms?"*

The analysis of baseline differences between depressed and non-depressed PD patients provided information on the variables that potentially should be taken into account in the longitudinal analysis. In the longitudinal analysis we found that female gender, more severe disability, more cognitive impairment, motor fluctuations, nighttime sleep problems, increased daytime sleepiness, more autonomic dysfunction (urinary and cardiovascular domains) and the use of antidepressants were independently associated with higher BDI scores over time (LMM).

Studies evaluating depression in PD have usually examined a limited number of clinical variables and the results among these studies were often inconclusive due to heterogeneity of sample compositions and the cross-sectional nature of the study designs. As a result, contradictory findings have been reported.

Female gender, more severe disability and lower cognition scores were variables found to be associated with more severe depressive symptoms, which is in agreement with results from two earlier longitudinal studies.[7,10] We further found that motor fluctuations, nighttime sleep problems and autonomic dysfunction were associated with depressive symptomatology, findings that only have been found in previous cross-sectional studies (Supplement 6.2 Table S6.3). We identified one other associated factor of depression, namely daytime sleepiness. Interestingly, this symptom, together with depression, cognitive decline, autonomic dysfunction, psychotic symptoms and PIGD were previously identified as components of a coherent predominantly non-dopaminergic (PND) symptom complex in PD.[37] Notably, this complex is prevalent early in the disease and worsens with disease progression,[21] which likely is the consequence of progressive α-synuclein aggregate-related synaptopathy and axon degeneration of the nervous system.[38-40] All five other components of the PND complex were associated with higher BDI scores over time, of which three made an independent contribution to the model (daytime sleepiness, cognitive impairment and autonomic dysfunction). Interestingly, compared to patients not on antidepressants, patients on antidepressants had higher BDI scores and suffered more advanced PD. [mean (SD) BDI 12.38 (7.02) vs 9.83 (6.42); p = .004]. Collectively, these findings suggest that progression of pathobiology is an important causative factor for depression in PD, which might be resistant to currently available treatment options for depression.

Motor fluctuations were also found to be associated with depressive symptoms and this complication of levodopa treatment usually increases in prevalence and severity as the progression of PD advances. In non-depressed PD patients motor fluctuations may be associated with mood fluctuations.[8] Since several effective strategies to target motor fluctuations are now available,[41] these approaches potentially may also have an impact on depressive symptoms in PD.

*"Which factors are associated with an increased risk of future depression?"*

Approximately 28% of patients who had no depression at baseline fulfilled the criteria for depression at least once during the course of the study (Figure 6.1). The presence of depression across these patients varied considerably each year, with approximately half of the cases showing persistent depression while the other half showed depression with a non-persistent pattern. Because of the potential overlap in somatic symptoms of depression and PD, we also examined if at least one or both of the two non-somatic symptoms that are essential for the clinical diagnosis of major depression,[42] i.e., feeling sad (item 1 of the BDI) and loss of pleasure (item 4), were present in those classified as depressed. This analysis showed that at least one of these features was present in 97% of patients who were classified as depressed (BDI >15) at baseline, and in 93% of patients who were classified as

depressed during follow-up. This indicates that non-somatic features were included the classification of depression in the vast majority of cases.

The survival analysis showed that higher baseline BDI scores, increased daytime sleepiness and higher levodopa dosage were risk factors for future depression. As mentioned earlier, a higher baseline BDI score was also an important predictor for a persisting form of depression. Similar to the findings by Becker et al., levodopa dose emerged as an independent risk factor for future depression in our study.[10] Interestingly, levodopa only emerged in the survival analysis and not the LMM. To date, however, the role of levodopa in depression of PD has remained controversial, with studies reporting effects varying from protection to deterioration.[43,44] Serotonin is a key factor in mood regulation and in a rat model long-term levodopa treatment decreased serotonin synthesis in the nucleus raphe dorsalis and other serotonergic regions in the brain.[45] We can therefore not exclude that over time, continued exposure to levodopa contributes to the development of depression in PD. The finding that daytime sleepiness is a predictor of future development of depression corresponds with our findings from the LMM analysis.

Of note is that 4–17% of all patients who were depressed were treated with antidepressants over the years of the study. Since no information was available on the efficacy of drugs used to treat depression in our cohort, the use of antidepressants was not considered in the classification of patients in the primary analysis of this study, although we controlled for use of this medication by including it as a covariate. In a secondary analysis patients who had a BDI < 15 but used antidepressants were also classified as depressed and this approach revealed similar results, supporting the robustness of the findings.

Of note is that the dopamine agonist pramipexole has been found to have antidepressant properties in a randomized clinical trial setting.[44] In our cohort, 26% of patients used this medication at baseline and this could have impacted the occurrence and course of depressive symptoms. We therefore performed an additional univariate LMM analysis where use of pramipexole (yes/no) was included as a separate variable and this analysis showed that this variable was not significantly associated with BDI scores over time [B(95%CI) = −0.18(−1.43 to 1.07), p = 0.78], which makes potential confounding by use of this dopamine agonist unlikely. The application of a cut-off score to classify patients as depressed or not depressed and the non-persistent course of depression could have contributed to the apparent discrepancy between the results of the LMM and the Cox Proportional Hazards model. Although both procedures involve analysis of longitudinal data, they provide different answers to different questions, namely: “Which factors are associated with longitudinal changes in depressive symptoms?” (LMM) vs “Which factors are associated with an increased risk of future depression in patients who are free of this condition at baseline?”

(survival analysis). In addition, data of all patients are used in the LMM analysis, whereas in the survival analysis only data of patients who are free of depression at baseline are used. The strengths of this study are the prospective design, the broad clinical characterization, the limited loss to follow-up and the size of the cohort. Limitations of our study relate to the fact that we were not knowledgeable of previously reported patient-specific baseline risk factors of depression, namely the occurrence of life events, personality traits, history of depression, pain or fatigue.[12,17] In addition, due to an overlap of symptoms of depression and PD, one could argue that it is not surprising that the severity of PD, or a higher baseline BDI score, would predict future BDI scores. However, we attempted to control this potentially distorting effect on our results using a PD-specific cut-off value for depression of the BDI and by applying a multivariate approach, where, amongst others, differences in baseline disease severity and duration were taken into account. At last, our cohort is hospital-based, which may have resulted in some over- or underestimation, although it seems unlikely that this has resulted in significant distortions of our conclusions.

In summary, in this prospectively studied cohort of patients with PD, depression is a common feature that may follow a persistent or a non-persistent course and occurs more often in female patients. Apart from motor fluctuations and levodopa dose, depressive symptoms in PD are mainly associated with factors of non-dopaminergic origin. This suggests that depression in PD is an inherent consequence of the progressive pathobiology of the disease, which may render its treatment with currently available treatment options difficult.

**SUPPLEMENT 6.1**

**Table S6.1:** Baseline data of patients with and without persisting depression

| | Total | Persisting depression | Non-persisting depression | p-values |
|---|---|---|---|---|
| N | 152 | 58 | 94 | |
| Age, yr | 61.73 (10.72) | 63.90 (11.11) | 60.39 (10.30) | .05[f] |
| Sex, % female | 40.1 | 50.0 | 34.0 | .05[a,f] |
| Antidepressants, % | 19.0 | 31.0 | 11.7 | .003[a,f] |
| Education, yr | 11.77 (4.09) | 11.11 (4.15) | 12.18 (4.02) | .12 |
| Disease duration, yr | 11.12 (5.77) | 12.42 (6.16) | 10.31 (5.40) | .03[f] |
| Age at onset, yr | 50.62 (10.38) | 51.49 (10.72) | 50.08 (10.19) | .42 |
| Hoehn & Yahr, stage | 3 (2,3) | 3 (2,4) | 2 (2,3) | .001[b,f] |
| SPES/SCOPA Motor Impairments | 13.88 (5.06) | 15.11 (5.40) | 13.12 (4.71) | .02[f] |
| SPES/SCOPA Dyskinesias | 1.16 (1.71) | 1.35 (1.78) | 1.04 (1.66) | .29 |
| SPES/SCOPA Motor Fluctuations | 1.04 (1.39) | 1.04 (1.29) | 1.04 (1.46) | .98 |
| SPES/SCOPA ADL | 9.59 (3.34) | 10.25 (3.59) | 9.18 (3.12) | .06 |
| Motor phenotype, PIGD dominant, % | 51.9 | 62.0 | 45.9 | .08[a] |
| Beck Depression Inventory | 14.22 (6.70) | 18.07 (6.77) | 11.85 (5.47) | <.001[f] |
| SCOPA-COG[c] | 24.91 (5.67) | 22.93 (5.90) | 26.09 (5.22) | .001[f] |
| SCOPA-SLEEP, NS[d] | 6.09 (3.86) | 6.50 (4.09) | 5.83 (3.72) | .30 |
| SCOPA-SLEEP, EDS[d] | 6.10 (3.95) | 6.71 (4.00) | 5.72 (3.90) | .14 |
| SCOPA-AUT, GI score[e] | 3.12 (3.19) | 3.36 (2.18) | 2.97 (2.19) | .28 |
| SCOPA-AUT, UR score[e] | 7.68 (4.01) | 8.40 (4.10) | 7.24 (3.91) | .08 |
| SCOPA-AUT, CV score[e] | 1.46 (1.30) | 1.63 (1.23) | 1.36 (1.33) | .22 |
| Hallucinations, % with | 23.1 | 26.9 | 20.9 | .41[a] |
| LDE-Dopa, mg/day | 451 (375) | 462 (370) | 445 (379) | .79 |
| LDE-DA dose, mg/day | 276 (231) | 262 (243) | 284 (225) | .56 |

*Only patients from whom at least 3 measurements were available are included in this table. Patients were considered to have a persisting form of depression if he or she was classified as depressed for more than 50% of the total number of assessments (i.e. BDI score ≥15) and a non-persisting form of depression if he or she was classified as depressed for lesser than or equal to 50% of the total number of assessments (i.e. BDI score <15).*

*Variables are expressed as means (standard deviations), except for gender, antidepressants, motor subtype, hallucinations (percentages) and Hoehn and Yahr stage (median ((interquartile range)). All differences are calculated with the independent-samples t-tests, except for [a] Chi-square test and [b] Mann-Whitney U test.*

*[c] SCOPA-COG: cognitive function, higher scores reflect better functioning.*
*[d] SCOPA-SLEEP, NS score: nighttime sleep problems; DS score: daytime sleepiness*
*[e] SCOPA-AUT: sumscore autonomic functioning including items from the sections on gastrointestinal (GI), cardiovascular (CV) and urinary tract (UR).*
*[f] Significant values*

*Abbreviations: ADL, activities of daily living; PIGD, postural instability gait difficulty; BDI, Beck depression inventory; DA, dopamine agonists.*

**SUPPLEMENT 6.2**

**Table S6.2:** Progression of scores on different domains for patients with persistent depression vs persistent non-depression, after adjusting for age, gender and disease duration

| Variable | B (95%CI) | P |
|---|---|---|
| SPES/SCOPA – Motor Impairment | 2.79 (1.64-3.94) | <.001[e] |
| SCOPA-COG score[a] | -3.52 (-5.00- -2.05) | <.001[e] |
| SPES/SCOPA – ADL | 2.45 (1.64-3.27) | <.001[e] |
| SPES/SCOPA – Motor Fluctuations | 1.01 (0.47-1.54) | <.001[e] |
| SPES/SCOPA – Dyskinesia | 0.39 (0.04-0.73) | .03[e] |
| PIGD score[b] | 1.60 (1.07-2.13) | <.001[e] |
| SCOPA-SLEEP-NS score[c] | 2.54 (1.73-3.35) | <.001[e] |
| SCOPA-SLEEP-DS score[c] | 2.37 (1.45-3.29) | <.001[e] |
| SCOPA-AUT[d] GI score | 0.67 (0.18-1.16) | .007[e] |
| SCOPA-AUT[d] UR score | 1.88 (1.01-2.76) | <.001[e] |
| SCOPA-AUT[d] CV score | 0.69 (0.42-0.97) | <.001[e] |
| SCOPA – PC[e] – Hallucinations | 0.23 (0.11-0.35) | <.001[e] |

*Estimates are presented as B with 95% confidence intervals (CI), where a positive value is associated with a positive relationship between persistent depression and the specified domain.*
*[a] SCOPA-COG: cognitive function, higher scores reflect better functioning.*
*[b] PIGD score: sumscore of postural-instability and gait disorder (problems with freezing, gait, postural stability and walking)*
*[c] SCOPA-SLEEP, DS: daytime sleepiness NS: Nighttime sleep problems*
*[d] SCOPA-AUT: sumscore autonomic functioning including items from the sections on gastrointestinal (GI), cardiovascular (CV) and urinary tract (UR).*
*[e] SCOPA-PC, hallucinations subscore of scale on psychiatric complications (PC)*
*[f] significant values*

**Table S6.3:** Risk factors associated with developing depression or depressive symptoms in PD

| Risk Factor | References from studies supporting association with depression | References from studies not supporting an association with depression |
|---|---|---|
| Older age | 6 | 2,7,12 |
| Female gender[b] | 1, 5[a],9 | 2,3 |
| Disease duration | 4[a],11 | |
| Severity motor symptoms | 2,4[a],7,8,11, 12 | 6,13 |
| Severity of disability (ADL)[b] | 1 | |
| PIGD dominant subtype | 11 | 3 |
| Motor fluctuations[b] | 2,11 | |
| Cognitive symptoms[b] | 1,2,11 | |
| Nighttime sleep problems[b] | 10,11 | |
| Daytime Sleepiness[b] | | |
| Autonomic symptoms[b] | 11,13 | |
| Levodopa dosage[b] | 2,5[a] | |
| Hallucinations | 11,14 | |

[a] *Risk factor observed in longitudinal study in existing literature (all other studies had a cross-sectioonal design);*
[b] *Factor associated with depressive symptoms or development of future depression confirmed by either LMM or survival analysis in the current study*

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Chapter 7:

# Onset and evolution of anxiety in Parkinson's disease


Kangdi Zhu[1]; Jacobus J. van Hilten[1]; Johan Marinus[1]

[1]Department of Neurology, Leiden University Medical Center, Leiden, The Netherlands

Published in *European Journal of Neurology* 2017;24:404-411

**ABSTRACT**

*Background.* Anxiety is common in Parkinson's disease (PD) and has great influence on quality of life. However, little is known about risk factors for development of anxiety in PD.

*Objectives.* To investigate which factors are associated with longitudinal changes in severity of anxiety symptoms and development of future anxiety in non-anxious patients at baseline.

*Methods.* Analyses were performed in data of the SCOPA-PROPARK cohort, a 5-year hospital-based longitudinal cohort of over 400 PD patients who have been examined annually. Linear mixed models was used to identify factors associated with longitudinal changes in Hospital Anxiety and Depression Scale – Anxiety (HADS-A) scores. Survival analysis using data of non-anxious patients at baseline was performed to identify predictors for future anxiety (i.e. HADS-A ≥11).

*Results.* Of 409 patients included at baseline, 67 (16%) had anxiety, whereas 64 (19%) of the remaining 342 non-anxious patients developed anxiety after a mean (SD) follow-up of 2.6 (1.3) years. Seventy percent of the patients with anxiety were also depressed. Female gender, cognitive impairment, depressive symptoms, dysautonomia, insomnia and excessive daytime sleepiness (EDS) at baseline were associated with higher HADS-A scores over time and, except for female gender and EDS, all these variables were independent predictors of development of anxiety in non-anxious patients at baseline. *Conclusions.* Anxiety is highly prevalent in PD. Higher anxiety scores over time and future development of anxiety are associated with female gender, cognitive impairment, autonomic dysfunction, insomnia and EDS. Anxiety and depression usually co-exist and share similar determinants, suggesting a common pathophysiological mechanism.

## INTRODUCTION

Anxiety and depression are common in Parkinson's disease (PD) and these features have profound consequences for a patient's health and mental well-being over the disease course.[1] A recent systematic review found an average point prevalence of anxiety disorders in PD of 31%.[2] Anxiety may be non-episodic and episodic in nature; it may vary with the severity of motor fluctuations and situational anxiety may be related to motor deficits caused by, for example, fear of falling due to freezing [3]. Anxiety and depression often co-occur in PD, and even though anxiety has a greater influence on the quality of life of PD patients,[1,4] studies in the past have mainly focused on depression and little is known about risk factors for anxiety in PD.

Most research on anxiety in PD has been cross-sectional in nature.[3,4,6-9] Similar to findings in the general population, these studies reported a more frequent occurrence of anxiety symptoms in female patients.[5] PD-specific factors found associated with anxiety include longer disease duration, younger age-at-onset, dysautonomia, motor fluctuations and impairment in activities of daily living.[3,4,6-8] Due to the heterogeneity of factors examined and the inconsistent findings across studies, definite conclusions regarding the role of some factors (e.g. disease severity, motor fluctuations) remain difficult.[3,4,6-8] Another disadvantage of cross-sectional studies is that the time relation between potential risk factors and emergence of anxiety is obscured. Hitherto, only one longitudinal study on anxiety in PD has been performed.[9] In this study, 89 mildly affected patients were followed over a relatively short period of 1.5 years. However, identification of risk factors ideally requires a large cohort that is followed up long enough until a sufficient number of anxiety cases has developed. The PROPARK cohort includes over 400 PD patients who have been examined annually and followed for five years.[10] This cohort is therefore well-suited to investigate which factors are associated with: 1) longitudinal changes in severity of anxiety symptoms; and 2) development of future anxiety in patients who are free of this symptom at baseline.

## METHODS

*Study design and participants*

The study design has been described in detail elsewhere.[10] In brief, patients were recruited from neurology clinics of university and regional hospitals in the western part of The Netherlands and all fulfilled the United Kingdom Parkinson's disease Society Brain Bank criteria for idiopathic PD.[11] In view of the fact that we aimed to obtain information on the full spectrum of the disease, a recruitment strategy based on age-at-onset (< or ≥50 years) and disease duration (< or ≥10 years) was applied, which resulted in four different strata that were aimed at containing at least 100 patients each.[10] In view of the fact that we aimed to obtain information on the full spectrum of the disease, a recruitment strategy based on age-at-onset (< or ≥50 years) and disease duration (< or ≥10 years) was applied, which resulted in four different strata that were aimed at containing at least 100 patients each.[10]

*Assessment of baseline variables*

At baseline (2003-2005) and the five subsequent annual visits all patients received standardized assessments. These included an evaluation of demographic and clinical characteristics, family history of PD, and registration of antiparkinsonian medication. A levodopa dose equivalent (LDE) of daily levodopa and dopamine agonists dose was calculated for each patient at baseline.[11] Diagnosis of PD and the patient's Hoehn & Yahr (H&Y) stage were ascertained at every assessment.[12]

The following instruments were administered by qualified examiners: the SPES/SCOPA[13] (including sections on motor examination, activities of daily living (ADL) and motor complications), SCOPA-COG (cognition),[14] and SCOPA-PC (psychotic symptoms).[15] All patients with dopaminergic medication were assessed during "on''. Motor subtype was determined by calculating a ratio of tremor score (SPES/SCOPA)[13] over PIGD score (SPES/SCOPA).[14] Patients with a ratio <1.0 were classified as PIGD-dominant, whereas those with values of ≥1.0 were classified as non-PIGD-dominant.[16]

Patients completed the following instruments: the SCOPA-AUT (autonomic domains: gastrointestinal, urinary tract and cardiovascular),[17] SCOPA-SLEEP (nighttime sleep [NS] and daytime sleepiness [DS])[18] and Beck Depression Inventory (BDI).[19] For all instruments except SCOPA-COG, higher scores reflect poorer functioning.

*Ascertainment of anxiety*

Anxiety was assessed using the anxiety subscale of the Hospital Anxiety and Depression Scale (HADS).[20] This scale focusses on the non-somatic features of anxiety and its clinimetric properties for use in PD are very satisfactory.[21] The HADS-A includes 7 items that measure severity of anxiety symptoms over the previous 2 weeks; all items are rated on a 4-

point scale (0-3), with higher scores indicating more severe anxiety. To minimize the number of false-positive cases and obtaining maximum certainty regarding the anxiety cases, a score of ≥11 was considered as 'having anxiety'.[21] To verify robustness of this method, all analyses have been repeated with a cut-off score of ≥8.

*Statistical analysis*

For objective 1 a linear mixed models (LMM) analysis was performed using data of all patients included in the follow-up. This method allows for the identification of variables that are associated with variations in HADS-anxiety scores over time. A restricted maximum likelihood model with an autoregressive (heterogeneous) covariance structure type was used in all LMM analyses and since heterogeneity between patients was expected in baseline levels and in change over time, random intercepts and random slopes were used. Variables that have been found associated with anxiety in earlier studies were considered in the LMM. H&Y stage was not included because it is partly determined by motor phenotype. BDI scores were not included in the primary LMM analysis due to the strong correlation with anxiety as found in earlier studies;[22] inclusion of such a strongly associated variable could obscure the relationship of anxiety with other potentially interesting variables. In addition, to determine the degree of correlation between anxiety and depression, depression rates were determined in patients with anxiety at baseline and in patients who developed anxiety during follow-up. In a secondary analysis, however, the effect of including the BDI score on the model was examined.[23] The relationship between variables that are associated with variation in HADS-anxiety scores over time were first analyzed including one variable at a time (unadjusted model). Subsequently an adjusted model was performed in which the main effects of all significant baseline variables from the unadjusted model were entered. The final model only includes variables that were significant from the adjusted model.

For objective 2 we performed a survival analysis in data of patients without anxiety at baseline using the same variables that were included in the LMM. Survival time was calculated as the difference in years between the date on which anxiety was first reported and the date of the patient's baseline assessment. Patients were considered to have an event ('uncensored') if they scored ≥11 on the HADS-anxiety scale. If a patient did not have an event during follow-up, he or she was 'withdrawn alive' and classified as 'censored'. In case a patient had missed one year and had no anxiety in the previous and following year, we assumed that the patient had not developed anxiety in that year. A similar approach as used for the LMM was employed to adjust for the potential influence of confounders. As before, the effect of including the baseline BDI score on the model was examined in a secondary analysis. Risk factors were calculated as hazard ratios (HR) with 95% confidence

intervals (CI), with a HR >1 indicating that a baseline variable was associated with a higher risk of developing anxiety.
Since antidepressant or benzodiazepine use might have a potential effect on anxiety severity, these variables were included as covariates in the LMM and survival analysis. Analyses were performed with the Statistical Package for the Social Sciences (SPSS) version 21.0.

**RESULTS**

Of the 409 patients at baseline, 67 (16%) were classified as suffering from anxiety, whereas 342 (84%) were not (figure 1). Of those not suffering from anxiety at baseline, 64 (19%) developed this symptom after a mean (SD) follow-up of 2.6 (1.3) years.

*Study Sample*

For details on the baseline study sample, see Table 7.1.

*Co-existing anxiety and depression*

Seventy percent of patients with anxiety at baseline also fulfilled the criteria for depression (BDI≥15). During follow-up of patients without anxiety at baseline (N=342), 43 of 64 (67%) patients who subsequently developed anxiety also qualified for depression. No additional survival analysis was performed on this group due to insufficient power.

**Figure 7.1**: Flow Chart of follow-up for anxiety

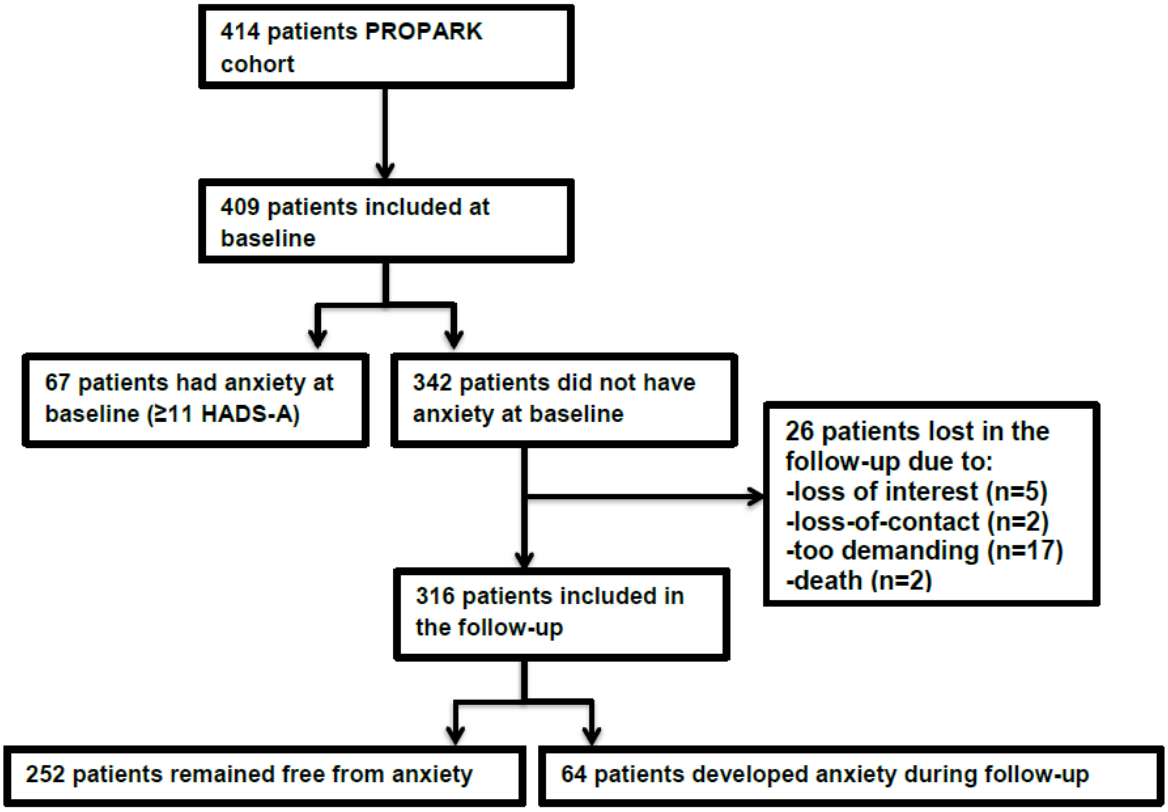

**Table 7.1:** Baseline data of patients with and without anxiety

| | Total | With anxiety | Without anxiety | p-values |
|---|---|---|---|---|
| N | 409 | 67 | 342 | |
| Age, yr | 61.14 (11.37) | 62.38 (12.85) | 60.86 (11.07) | .32 |
| Sex, % female | 35.9 | 55.2 | 32.2 | <.001[a] |
| Age at onset, yr | 50.53 (11.89) | 51.56 (12.08) | 50.35 (11.89) | .45 |
| Disease duration, yr | 10.62 (6.53) | 10.82 (5.94) | 10.50 (6.62) | .71 |
| Hoehn & Yahr, stage | 2 (2,3) | 3 (2,4) | 2 (2,3) | <.001[b] |
| SPES/SCOPA-Motor Impairment | 13.49 (4.95) | 15.10 (5.42) | 13.16 (4.79) | .004 |
| SPES/SCOPA-Dyskinesia | 0.94 (1.62) | 0.94 (1.52) | 0.93 (1.62) | .96 |
| SPES/SCOPA-Motor Fluctuations | 0.78 (1.26) | 1.09 (1.47) | 0.70 (1.19) | .04 |
| SPES/SCOPA-ADL | 8.92 (3.56) | 9.75 (3.97) | 8.71 (3.45) | .03 |
| PIGD dominant phenotype, % | 44.2 | 58.1 | 39.9 | .008[a] |
| BDI score | 10.21 (6.57) | 18.17 (7.25) | 8.64 (5.22) | <.001 |
| No. (%) meeting depression criteria | 86 (21.0) | 46 (68.7) | 40 (11.7) | <.001[a] |
| HADS Anxiety score | 6.54 (3.63) | 12.73 (1.68) | 5.33 (2.49) | <.001 |
| SCOPA-COG score[c] | 25.71 (6.21) | 23.41 (5.63) | 26.21 (6.21) | .001 |
| SCOPA-SLEEP-NS score[d] | 4.51 (3.77) | 6.15 (4.30) | 4.17 (3.57) | .001 |
| SCOPA-SLEEP-DS score[d] | 4.87 (3.73) | 6.20 (3.70) | 4.62 (3.70) | .002 |
| SCOPA-AUT, GI score[e] | 2.72 (2.20) | 3.79 (2.36) | 2.50 (2.11) | <.001 |
| SCOPA-AUT, CV score[e] | 1.16 (1.19) | 1.76 (1.30) | 1.02 (1.10) | <.001 |
| SCOPA-AUT, UR score[e] | 6.72 (4.02) | 8.39 (4.48) | 6.36 (3.81) | .001 |
| Hallucinations, % with | 16.5 | 29.0 | 14.2 | .004[a] |
| Antidepressants, % with | 14.7 | 23.9 | 12.9 | .02[a] |
| Benzodiazepine, % with | 22.1 | 44.8 | 17.6 | <.001[a] |
| Total LDE, mg/day | 608 (463) | 575 (395) | 609 (475) | .54 |
| LDE-Dopa, mg/day | 380 (375) | 367 (342) | 378 (381) | .82 |
| LDE-DA dose, mg/day | 231 (226) | 208 (218) | 233 (227) | .42 |

*Variables are expressed as means (standard deviations), except for gender (percentages), motor subtype (percentages), Hoehn and Yahr stage (median ((interquartile range)). All differences are calculated with the independent-samples t-tests, except for*
*a Chi-square test and b Mann-Whitney U test.*
*c SCOPA-COG: cognitive function, higher scores reflect better functioning.*
*d SCOPA-SLEEP, NS score: nighttime sleep problems; DS score: daytime sleepiness*
*e SCOPA-AUT: sumscore autonomic functioning including items from the sections on gastrointestinal (GI), cardiovascular (CV) and urinary tract (UR).*
*Abbreviations: DBS, Deep Brain Surgery; ADL, activities of daily living; PIGD, postural instability gait difficulty; BDI, Beck depression inventory; LDE, Levodopa dosage equivalent; DA, dopamine agonists.*

*Variables associated with longitudinal changes in HADS-anxiety score (LMM analysis)*
The final model of the LMM analysis showed that female gender, more cognitive impairment, and more severe insomnia, EDS and dysautonomia at baseline were associated with higher HADS-anxiety scores over time (Table 7.2). The secondary analysis including the BDI-score showed that baseline BDI-score was associated with higher anxiety scores over time in the final analysis (B (95%CI)=0.28 (0.24-0.32), p<.001). Female gender, cognitive dysfunction and the cardiovascular domain of autonomic dysfunction remained significant, while insomnia and the gastrointestinal domain of autonomic dysfunction did not, suggesting a strong shared covariance between these two factors and depression.

*Risk factors for future development of anxiety (survival analysis)*
The multivariate Cox proportional hazards' model showed that more cognitive impairment, insomnia and autonomic dysfunction (cardiovascular domain) were independent predictors for future development of anxiety in patients not suffering from anxiety at baseline (Table 7.3).
The secondary analysis including the baseline BDI-score showed that baseline BDI-score was an independent predictor of anxiety (HR(95%CI)=1.12 (1.07-1.17), p<.001). Insomnia and the cardiovascular domain of autonomic dysfunction remained significant, while cognitive impairment did not. Repeating the analysis with a cut-off score of ≥8 showed that the same variables emerged as significant in the final model (Table 7.4).

**Table 7.2:** Factors associated with higher HADS-A scores over time in patients with PD

| | Unadjusted Model | | Adjusted Model | | Final Model | |
|---|---|---|---|---|---|---|
| **Variable** | **B (95%CI)** | **P** | **B (95%CI)** | **P** | **B (95%CI)** | **P** |
| Age | 0.04 (0.01-0.06) | .01[d] | -0.03 (-0.06-0.01) | .04[d] | -0.03 (-0.05-0.01) | .05 |
| Female gender | 1.37 (0.73-2.02) | <.001[d] | 0.72 (0.10-1.34) | .02[d] | 0.67 (0.12-1.22) | .02[d] |
| Disease duration in years | 0.05 (0.01-0.10) | .04[d] | -0.07(-0.12- -0.02) | .01[d] | -0.04 (-0.08-0.01) | .05 |
| SPES/SCOPA–Motor Impairment | 0.18 (0.12-0.24) | <.001[d] | 0.07 (-0.01- 0.15) | .10 | | |
| SPES/SCOPA – ADL | 0.29 (0.20-0.37) | <.001[d] | 0.01 (-0.12-0.15) | .85 | | |
| SPES/SCOPA – Dyskinesia | 0.28 (0.09-0.48) | .01[d] | 0.01 (-0.20-0.23) | .89 | | |
| SPES/SCOPA – Motor Fluctuations | 0.51 (0.26-0.76) | <.001[d] | 0.20 (-0.07-0.47) | .15 | | |
| PIGD dominant phenotype | 1.49 (0.85-2.13) | <.001[d] | 0.23 (-0.39-0.86) | .47 | | |
| SCOPA-COG score[a] | -0.16 (-0.21--0.11) | <.001[d] | -0.11(-0.16- -0.05) | <.001[d] | -0.11(-0.16- -0.06) | <.001[d] |
| Presence of hallucinations | 1.92 (1.09-2.75) | <.001[d] | 0.66 (-0.13-1.44) | .10 | | |
| SCOPA-SLEEP-NS score[b] | 0.28 (0.21-0.36) | <.001[d] | 0.10 (0.02-0.19) | .02[d] | 0.15 (0.07-0.22) | <.001[d] |
| SCOPA-SLEEP-DS score[b] | 0.26 (0.16-0.33) | <.001[d] | 0.09 (0.01-0.18) | .03[d] | 0.13 (0.05-0.20) | .001[d] |
| SCOPA-AUT[c] GI score | 0.52 (0.38-0.66) | <.001[d] | 0.17 (0.01-0.32) | .03[d] | 0.18 (0.05-0.31) | .01[d] |
| SCOPA-AUT[c] CV score | 1.16 (0.92-1.41) | <.001[d] | 0.61 (0.34-0.89) | <.001[d] | 0.66 (0.42-0.90) | <.001[d] |
| SCOPA-AUT[c] UR score | 0.27 (0.20-0.35) | <.001[d] | 0.06 (-0.02-0.15) | .13 | | |
| Daily levodopa dose, p/100mg | 0.15 (0.06-0.23) | .001[d] | -0.01 (-0.01-0.01) | .88 | | |
| Daily DA dose, p/100 mg | -0.03 (-0.17-0.11) | .71 | | | | |
| Use of benzodiazepines, yes/no[e] | 2.44 (1.71-3.16) | <.001[d] | 0.94 (0.21-1.67) | .01[d] | 1.15 (0.47-1.84) | .001[d] |
| Use of antidepressants, yes/no[e] | 1.89 (1.02-2.76) | <.001[d] | 1.47 (0.67-2.28) | <.001[d] | 1.22 (0.47-1.98) | .002[d] |

*Estimates are presented as B with 95% confidence intervals (CI), where a positive value is associated with a positive relationship between the baseline variable and HADS-A scores.*
*Abbreviations: HADS-A, Hospital Anxiety and Depression Scale-Anxiety; ADL, activities of daily living; PIGD, postural instability gait difficulty; DA, dopamine agonists.*

[a] *SCOPA-COG: cognitive function, higher scores reflect better functioning.*
[b] *SCOPA-SLEEP, NS score: nighttime sleep problems. DS score: daytime sleepiness*
[c] *SCOPA-AUT: sumscore autonomic functioning including items from the sections on gastrointestinal (GI), cardiovascular (CV) and urinary tract (UR).*
[d] *significant values*
[e] *these variables were only included as a covariate in a secondary LMM analysis to correct for possible confounding effect of medication use. exact same variables were significant from the final analysis.*

**Table 7.3:** Longitudinal risk factor analysis of the development of anxiety (≥11 HADS-A) in patients without anxiety at baseline

| | Unadjusted Model | | Adjusted Model | | Final Model | |
|---|---|---|---|---|---|---|
| | **HR (95%CI)** | **P** | **HR (95%CI)** | **P** | **HR(95%CI)** | **P** |
| Age, p/yr increase | 1.03 (1.01-1.05) | .01[d] | 1.01 (0.98-1.04) | .68 | | |
| Gender, HR for females | 1.54 (0.94-2.52) | .09 | | | | |
| Disease duration, p/yr increase | 1.03 (0.99-1.07) | .11 | | | | |
| SPES/SCOPA – Motor Impairment | 1.09 (1.04-1.15) | .001[d] | 1.01 (0.94-1.09) | .77 | | |
| SPES/SCOPA – ADL | 1.16 (1.08-1.25) | <.001[d] | 1.10 (0.95-1.27) | .22 | | |
| SPES/SCOPA – Dyskinesia | 1.23 (1.09-1.40) | .001[d] | 0.99 (0.83-1.17) | .89 | | |
| SPES/SCOPA – Motor Fluctuations | 1.20 (1.00-1.45) | .05 | | | | |
| Motor phenotype, HR for PIGD dominant | 1.68 (0.99-2.84) | .05 | | | | |
| SCOPA-COG[a], p/point increase | 0.93 (0.89-0.97) | .001[d] | 0.94 (0.89-0.99) | .03[d] | 0.93 (0.89-0.97) | .002[d] |
| Presence of hallucinations, yes/no | 2.25 (1.24-4.09) | .008[d] | 1.34 (0.68-2.64) | .40 | | |
| SCOPA-SLEEP-NS[b], p/point increase | 1.17 (1.10-1.24) | <.001[d] | 1.11 (1.03-1.20) | .006[d] | 1.15 (1.08-1.23) | <.001[d] |
| SCOPA-SLEEP-DS[b], p/point increase | 1.09 (1.03-1.16) | .003[d] | 1.00 (0.93-1.07) | .92 | | |
| SCOPA-AUT, GI[c] score p/point increase | 1.27 (1.15-1.41) | <.001[d] | 1.07 (0.96-1.21) | .24 | | |
| SCOPA-AUT, CV[c] score p/point increase | 1.72 (1.43-2.08) | <.001[d] | 1.35 (1.06-1.72) | .02[d] | 1.45 (1.18-1.79) | <.001[d] |
| SCOPA-AUT, UR[c] score p/point increase | 1.13 (1.07-1.20) | <.001[d] | 1.05 (0.96-1.11) | .37 | | |
| Daily levodopa dose, p/100mg increase | 1.10 (1.03-1.16) | .003[d] | 0.96 (0.89-1.04) | .29 | | |
| Daily DA dose, p/100 mg increase | 1.04 (0.94-1.16) | .43 | | | | |
| Use of benzodiazepines, yes/no[e] | 2.00 (1.14-3.49) | .02[d] | 1.09 (0.56-2.13) | .80 | | |
| Use of antidepressants, yes/no[e] | 1.65 (0.88-3.01) | .12 | | | | |

*All variables are expressed as hazard ratio (HR) with 95% confidence interval (CI).*
*Abbreviations: ADL, activities of daily living; PIGD, postural instability gait difficulty; BDI, Beck depression inventory; DA, dopamine agonists.*

*a SCOPA-COG: cognitive function, higher scores reflect better functioning.*
*b SCOPA-SLEEP, NS score: nighttime sleep problems. DS score: daytime sleepiness.*
*c SCOPA-AUT: sumscore autonomic functioning including items from the sections on gastrointestinal (GI), cardiovascular (CV) and urinary tract (UR).*
*d significant values*
*[e] these variables were only included as a covariate to correct for possible confounding effect of medication use*

**Table 7.4:** Longitudinal risk factor analysis of the development of anxiety (≥8 HADS-A)* in patients without anxiety at baseline

| | Unadjusted Model | | Adjusted Model | | Final Model | |
|---|---|---|---|---|---|---|
| | **HR (95%CI)** | **P** | **HR (95%CI)** | **P** | **HR(95%CI)** | **P** |
| Age, p/yr increase | 1.02 (1.01-1.04) | .01[d] | 1.00 (0.97-1.02) | .86 | | |
| Gender, HR for females | 1.08 (0.71-1.64) | .74 | | | | |
| Disease duration, p/yr increase | 1.01 (0.98-1.04) | .44 | | | | |
| SPES/SCOPA – Motor Impairment | 1.06 (1.01-1.11) | .02[d] | 1.04 (0.97-1.11) | .34 | | |
| SPES/SCOPA – ADL | 1.08 (1.02-1.15) | .01[d] | 0.98 (0.88-1.10) | .75 | | |
| SPES/SCOPA – Dyskinesia | 1.12 (1.00-1.26) | .06 | | | | |
| SPES/SCOPA – Motor Fluctuations | 1.01 (0.84-1.21) | .96 | | | | |
| Motor phenotype, HR for PIGD dominant | 1.01 (0.64-1.59) | .97 | | | | |
| SCOPA-COG[a], p/point increase | 0.94 (0.91-0.97) | .001[d] | 0.95 (0.91-0.99) | .03[d] | 0.94 (0.91-0.98) | .001[d] |
| Presence of hallucinations, yes/no | 1.65 (0.92-2.97) | .10 | | | | |
| SCOPA-SLEEP-NS[b], p/point increase | 1.09 (1.03-1.14) | .002[d] | 1.08 (1.02-1.15) | .008[d] | 1.09 (1.04-1.15) | .001[d] |
| SCOPA-SLEEP-DS[b], p/point increase | 1.10 (1.05-1.16) | <.001[d] | 1.06 (1.00-1.12) | .06 | | |
| SCOPA-AUT, GI[c] score p/point increase | 1.19 (1.08-1.30) | <.001[d] | 1.07 (0.96-1.18) | .24 | | |
| SCOPA-AUT, CV[c] score p/point increase | 1.41 (1.18-1.69) | <.001[d] | 1.33 (1.07-1.64) | .01[d] | 1.30 (1.07-1.59) | .008[d] |
| SCOPA-AUT, UR[c] score p/point increase | 1.09 (1.03-1.15) | .002[d] | 1.00 (0.94-1.07) | .96 | | |
| Daily levodopa dose, p/100mg increase | 1.08 (1.03-1.14) | .004[d] | 1.04 (0.98-1.11) | .20 | | |
| Daily DA dose, p/100 mg increase | 0.97 (0.89-1.06) | .55 | | | | |
| Use of benzodiazepines, yes/no[e] | 1.58 (0.94-2.64) | .08 | | | | |
| Use of antidepressants, yes/no[e] | 0.95 (0.51-1.79) | .88 | | | | |

*All variables are expressed as hazard ratio (HR) with 95% confidence interval (CI).*
*Abbreviations: ADL, activities of daily living; PIGD, postural instability gait difficulty; BDI, Beck depression inventory; DA, dopamine agonists.*

**At baseline, 138 patients were classified as anxious (HADS-A≥8). 271 patients were included in the follow-up analysis, of whom 96 (35%) developed this symptom after a mean (SD) follow-up of 2.3 (1.3) years.*

*[a] SCOPA-COG: cognitive function, higher scores reflect better functioning.*
*[b] SCOPA-SLEEP, NS score: nighttime sleep problems. DS score: daytime sleepiness.*
*[c] SCOPA-AUT: sumscore autonomic functioning including items from the sections on gastrointestinal (GI), cardiovascular (CV) and urinary tract (UR).*
*[d] significant values*
*[e] these variables were only included as a covariate to correct for possible confounding effect of medication use*

## DISCUSSION

We found a baseline prevalence rate for anxiety of 16%, which is lower than earlier reported rates.[4,6,7] One potential explanation for this finding is that we used a more conservative cut-off of 10/11 ('probable anxiety') instead of 7/8 ('possible anxiety'), which could have led to an underestimation. In addition, other studies applied different tools.[7] Of note is that if we applied the lower cut-off of 7/8, the prevalence rate would have been 34%, which corresponds with those from earlier studies.[6,7]

An important strength is that our study is the largest longitudinal study on this subject so far.[6-9] Interestingly, predictors of anxiety that emerged from this study corroborate with those identified in our study on predictors of depression.[23] The finding of a common set of predictors for both conditions along with the fact these disorders co-occurred in 70% of the patients, hints at a shared pathophysiological pathway. Earlier studies also reported co-occurrence of anxiety and depression in 14-41% of PD patients.[4,6-8] In addition, our second LMM analysis with the BDI score included, showed that depressive symptoms were significantly associated with higher anxiety scores over time in the final LMM analysis and survival analysis. Together these findings support the assumption that anxiety and depression share a common pathophysiological mechanism.

Our study identified dysautonomia, i.e. cardiovascular and gastrointestinal dysfunction, as risk factors of anxiety in PD. An association between anxiety and dysautonomia in PD was found in an earlier study, in which the authors compared the prevalence of dysautonomia in 32 PD patients and healthy controls, and examined the relation with anxiety and depression.[8] Our study confirms that this relationship is also present longitudinally, which may reflect an association by environment since anxiety and certain autonomic symptoms (e.g. sweating, dizziness, palpitations) frequently co-occur.[24] Moreover, dysautonomia is a criterion for the diagnosis of panics attacks.[25] In agreement with most earlier studies, severity of motor impairment and disability were not associated with severity of anxiety over time.[3,7]

We further found that EDS and cognitive dysfunction were longitudinally associated with anxiety symptoms. Previous studies on anxiety in PD did not evaluate cognition or excluded patients with cognitive dysfunction,[26] rendering any conclusion on the relation between cognition and anxiety in PD difficult. However, findings of earlier studies show that depressive symptoms are part of a robust coherent complex of features (cognitive dysfunction, EDS, hallucinations, dysautonomia, and PIGD), which largely do not improve on dopaminergic medication. This complex of predominantly nondopaminergic (PND) features, which is present early in the disease course and worsens with advancing disease, are assumed to reflect progression of Lewy body pathology in the peripheral and central nervous system.[27,28] Against this background, the strong relation between anxiety and depression,

likely suggests that anxiety is yet another component of this PND symptom complex. Collectively, our findings suggest that patients harboring manifestations of the PND complex are more likely to develop anxiety.

Since patients in our cohort were treated with best clinical practice, it is not surprising that 45% of all patients with anxiety at baseline were treated with benzodiazepines and 24% were treated with antidepressants. Although we corrected antidepressant/benzodiazepine use in our analyses, an underestimation of anxiety symptoms still might have occurred.

Limitations of our study relate to the fact that our cohort is hospital-based, which may have resulted in some under- or overestimation, although it seems unlikely that this has led to significant distortion of our conclusions. Another limitation is that we did not establish the anxiety diagnosis according to the Diagnostic and Statistical Manual of Mental disorders criteria,[25] which precluded the identification of the subcategory of anxiety disorder (e.g. social phobia). It may also have led to misclassification of patients in the survival analysis, but we have no reasons to assume that any potential misclassification is systematic, and, given that non-differential misclassification of a dichotomous variable will always bias the effect, if there is one, towards the null value, some effects may have been underestimated, but not overestimated.

In conclusion, anxiety is highly prevalent in PD. Female patients with cognitive impairment, autonomic dysfunction, insomnia and EDS are at risk to develop more severe anxiety symptoms. Anxiety and depression usually co-exist and share similar determinants, which suggest a common pathophysiological mechanism.

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# Chapter 8:

# Summary, concluding remarks and future perspectives

In this thesis, longitudinal analyses have been performed on the PROPARK-Cohort, a hospital-based cohort of 421 patients followed for a period of five years. The main focus of this thesis was to determine which predictors and associated factors contributed to the development of certain non-motor symptoms in Parkinson's disease (PD). Strengths of our cohort study include the length of the follow-up period, broad clinical characterization, limited loss-to-follow-up and the large cohort size. The following non-motor symptoms have been addressed in this thesis: psychosis (hallucinations), dementia, excessive daytime sleepiness (EDS), insomnia, depression and anxiety.

**Chapter 1** is the introduction of this thesis that describes the history of PD, its disease course and the challenges in current treatment methods for motor symptoms. In addition, a short introduction is presented regarding the different non-motor symptoms and their potential impact on the quality of life of patients with PD.
In the second part of this chapter, the aims are described and an outline of the non-motor symptoms addressed in this thesis is given. The importance of differentiating and identifying patients at risk to develop certain non-motor symptoms is illustrated, so that caregivers can better anticipate and recognize these symptoms. Furthermore, an overview of the different statistical methods applied in our analyses to identify risk factors of certain non-motor symptoms is provided. Chapter 1 ends with a chapter outline, in which the findings and shortcomings of past studies on this subject are presented.

**Chapter 2** presents the main predictors for the development of hallucinations in PD. Twenty-one percent of the patients in our cohort had hallucinations at baseline, whereas 46% of the patients without hallucinations at baseline developed this feature during follow-up. We found that hallucinations in PD are caused by a combination of interacting risk factors that are associated with older age and more advanced disease.
In addition, longer disease duration, more severe depressive and autonomic symptoms, cognitive impairment, sleep disturbances and higher levodopa dose were associated with the development of hallucinations. This indicates that patients with these characteristics must be followed-up more carefully for the development of hallucinations. If these symptoms occur, adjustments of the medication regimen should be considered to prevent the development of psychosis. The identification of female sex as a risk factor for developing of hallucinations in PD was a new finding and should be verified in future studies.

In **chapter 3,** we report on the predictors for dementia in PD. Dementia is a frequent and devastating development in PD. Some longitudinal studies in PD have reported prevalence rates as high as 80-100% in cases that were followed up for 20 years.[1] In our cohort, thirty-

two percent of patients had dementia at baseline, while 26% of patients without dementia at baseline developed dementia within a follow-up period of five years. Similar to our findings regarding hallucinations in the previous chapter, we found that the onset of dementia in PD involves a combination of potentially interacting risk factors that are associated with higher age and more advanced disease. Motor symptoms such as postural instability and gait difficulty (PIGD), dyskinesias and non-dopaminergic symptoms such as autonomic dysfunction, EDS, hallucinations and depression are predictors of dementia in patients with PD.

The objective of **chapter 4** is to examine persistency, cross-sectional and longitudinal associations, and risk factors for EDS in patients with PD. Our cohort had a baseline prevalence rate of EDS of 43%, while 46% of the patients without EDS at baseline developed this symptom during follow-up. In addition, EDS was found to be a non-persistent symptom, although the persistency and the proportion of patients with EDS increased with longer follow-up. Male gender, insomnia, cognitive and autonomic dysfunction, hallucinations, less severe dyskinesias, dose of dopamine agonists and use of antihypertensives were associated with more severe EDS over time, while use of benzodiazepines was associated with less severe EDS symptoms. More EDS symptoms and a PIGD-dominant phenotype were risk factors for future EDS. These findings suggest that with longer disease duration, a large proportion of patients develop EDS. Some risk factors such as dose of dopamine agonists and the use of antihypertensives are modifiable, and patients with risk factors should be monitored to improve quality of life and reduce risk of harm.

**Chapter 5** focuses on the course and factors associated with longitudinal changes in insomnia severity in patients with PD. Insomnia is a debilitating symptom in PD that has been scarcely investigated in a longitudinal design. Knowledge of factors associated with occurrence of insomnia may provide clues for an increased understanding of underlying pathophysiology and facilitate early detection. Linear mixed models (LMM) were used to identify factors associated with longitudinal changes in severity of insomnia symptoms and a generalized estimating equations (GEE) analysis was performed to determine which baseline variables were associated with the different aspects of insomnia (sleep initiation or maintenance difficulty). In our cohort, SCOPA-SLEEP-Nighttime Sleep (NS) scores were available for 412 patients at baseline, of whom 110 (27%) had insomnia (i.e. SCOPA-SLEEP-NS score ≥7). Of the remaining 302 patients, 99 (33%) developed insomnia at some point during follow-up. We found that more severe depressive symptoms, motor fluctuations, higher dopamine agonist doses and sleep medication use were independently associated

with more insomnia symptoms over time. The GEE analysis did not identify an unique set of determinants that affected specific aspects of insomnia.

The objective of **chapter 6** is to determine associated and predictive factors of depression in patients with PD. Depression is a common non-motor symptom in PD. Several studies identified depression as the main determinant of a poor quality of life in this population.[2,3] A major challenge for the diagnosis of depression in PD is the overlap of the symptoms associated with depression and the primary symptoms of PD (e.g. masked facies, slowness of movement, fatigue, weight change, loss of concentration, hyper- or insomnia).[4] Increased knowledge of associated and risk factors of depression in PD may facilitate its early detection, provide insight into the nature of this condition, and guide future intervention strategies. We found that the proportion of patients with depression was approximately 20% at baseline and that it remained stable during follow-up, with approximately half of the cases showing a persistent course. Female gender, more severe disability, more severe motor fluctuations, autonomic and cognitive dysfunction, insomnia and EDS were independently associated with more depressive symptoms over time. More baseline depressive symptoms, EDS and a higher levodopa dosage were risk factors for future depression. From these findings we can conclude that apart from motor fluctuations and levodopa dose, depressive symptoms in PD are mainly associated with factors of non-dopaminergic origin. This suggests that depression in PD is an inherent consequence of the progressive pathobiology of the disease, which may explain why treatment with currently available options is difficult.

The purpose of the study described in **chapter 7** is to evaluate which characteristics are associated with longitudinal changes in anxiety in PD. A recent systematic review found an average point prevalence of anxiety disorders in PD of 31%.[5] It is a common symptom in this population and has great influence on quality of life. However, little is known about risk factors for development of anxiety in PD. In this study, LMM was used to identify factors associated with longitudinal changes in Hospital Anxiety and Depression Scale – Anxiety (HADS-A) scores. In addition, survival analysis using data of non-anxious patients at baseline was performed to identify predictors for future anxiety (i.e. HADS-A≥11). Of the 409 patients with a HADS-A score available at baseline, 67 (16%) had anxiety, whereas 64 (19%) of the remaining 342 non-anxious patients developed anxiety after a mean follow-up of 2.6 years. Seventy percent of the patients with anxiety were also depressed. Female gender, cognitive impairment, depressive symptoms, autonomic dysfunction, insomnia and EDS at baseline were associated with more anxiety symptoms over time and, except for female gender and EDS, all these variables were also independent predictors of development of anxiety in non-anxious patients at baseline. Our findings suggest that the

future development of anxiety is associated with female gender, cognitive impairment, autonomic dysfunction, insomnia and EDS. In addition, anxiety and depression usually co-exist and share similar determinants, suggesting a common pathophysiological mechanism.

An overview of the most important longitudinal associations and risk factors described in this thesis is presented in Table 8.1.

**Table 8.1:** Overview of the results on longitudinal associations of non-motor symptoms in PD*

| Outcome | Variables from survival analysis[a] | Variables from LMM[b] |
|---|---|---|
| Hallucinations[c] | Female gender<br>↑ Age-at-onset<br>Dyskinesias<br>EDS<br>Autonomic dysfunction | Female gender<br>↑ Age-at-onset<br>Dyskinesias<br>EDS<br>Autonomic dysfunction |
| Dementia[d] | ↑ Age<br>↓ Education<br>EDS<br>↑ Levodopa dose | ↑ Age<br>↓ Education<br>EDS<br>PIGD<br>↑ Levodopa dose |
| EDS | Baseline EDS<br>PIGD dominant phenotype<br>Autonomic dysfunction (UR)<br>Antihypertensive medication | Male gender<br>↓ Dyskinesias<br>Cognitive impairment<br>Hallucinations<br>Insomnia<br>Autonomic dysfunction (UR, GI)<br>↑Dopamine agonists dose<br>Antihypertensive medication<br>Not using benzodiazepines |
| Insomnia[e] | Depressive symptoms | Motor fluctuations<br>Depressive symptoms<br>↑Dopamine agonists dose<br>Use of sleep medication |
| Depression | Baseline depressive symptoms<br>EDS<br>↑ Levodopa dose | Female gender<br>ADL impairment<br>Motor fluctuations<br>Cognitive impairment<br>Insomnia<br>EDS<br>Autonomic dysfunction (CV,UR)<br>Antidepressant use |
| Anxiety | Cognitive impairment<br>Insomnia<br>Autonomic dysfunction (CV) | Female gender<br>Cognitive impairment<br>Insomnia<br>EDS<br>Autonomic dysfunction (GI, CV)<br>Antidepressant use<br>Benzodiazepine use |

*Abbreviations: LMM, linear mixed models; EDS, excessive daytime sleepiness; PIGD, postural instability gait difficulty; UR, urinary tract; GI, gastrointestinal; CV, cardiovascular; ADL, activities of daily living*

**All variables are listed in descending order of the strength of association with a certain non-motor symptom*

[a]*Which factors are associated with an increased risk to develop a certain symptom in patients who are free of this symptom at baseline?*
[b]*Which factors are associated with longitudinal changes in the severity of a certain symptom?*
[c]*Original manuscript (Chapter 2) did not include a LMM analysis; LMM analysis yielded the same results as the survival analysis.*
[d]*Original analysis described in chapter 3 did not include a LMM analysis; LMM analysis yielded the same results as the survival analysis, except for PIGD as an additional finding.*
[e]*Survival analysis not described in the original publication. After performing the survival analysis, only depressive symptoms was significantly associated with insomnia.*

**Concluding remarks**

This thesis is based on analyses of data from a large longitudinal cohort of 421 PD patients, followed-up over a period of five years. Survival analysis and linear mixed models (LMM) were applied to identify baseline predictors for the development of a certain non-motor symptom over time. In essence, we tried to find answers to two questions, namely: "Which factors are associated with longitudinal changes in the severity of a certain symptom?" (LMM); and "Which factors are associated with an increased risk to develop a certain symptom in patients who are free of this symptom at baseline?" (Survival analysis). The first method (LMM) gives us a more complete view of factors associated with the variation of a certain symptom over time. The main advantages of this method is that we could use the data from all of our patients in the cohort and that it can deal missing outcomes in data. The second method (survival) is especially interesting from a clinical perspective, because it identifies which factors are responsible for the development of a certain symptom in patients who do not have that symptom at baseline. A potential disadvantage of this method is that a cut-off score has to be used to classify patients. Using a cut-off score to classify patients renders the risk of potential misclassification (over- or underestimation of potential predictors) since individual patient's scores may fluctuate around the cut-off.

At the start of this project, the focus of our studies was on survival analysis. Subsequently it became clear that both methods are complementary. When applied in combination, both methods provide a more comprehensive view of the longitudinal course of particular symptoms. Consequently, LMM was not applied in the original journal publications of chapter 2 (hallucinations) and chapter 3 (dementia). However, after applying the LMM analyses, similar results were found by both methods for these two symptoms, supporting the robustness of our initial findings. The application of a cut-off score also resulted in lower prevalence rates for anxiety and depression in our study. This difference can also be explained by the fact that other studies used different assessment methods to evaluate both symptoms in PD. For anxiety, some studies applied the Diagnostic Mental Manual criteria (DSM) to classify patients.[6] Though this could give a more accurate diagnosis of anxiety and allows identifying the specific subcategory of anxiety disorder (e.g. social phobia, panic disorder), it does not provide information regarding the severity of the symptoms. Another explanation for the lower prevalence rate for anxiety in our study could be the fact that we applied a more conservative cut-off of 10/11 ('probable anxiety') instead of 7/8 ('possible anxiety'), which could have led to an underestimation of anxiety rates in our study.

When interpreting the results of our analyses it is important to consider the composition of our study population. Our study is hospital-based and not population-based, and we applied

a pre-stratification strategy based on age-at-onset and disease duration. This may have affected the prevalence, the severity of certain symptoms and therefore the generalizability of our findings. However, the objective of our study was not to calculate the incidence proportion of a certain non-motor symptom, but to identify predictors for the development of this symptom. We cannot rule out that the increase in variation in age-at-onset and disease duration caused by our sampling strategy may have affected the strengths of the identified relations to some extent if compared to what would have been found in a population-based sample. Still, most associations found in our study, were quite strong. Hence it is unlikely that a selection bias may have contributed to the identification of predictors that are not generalizable to other populations. For instance, the predictors we described for EDS in chapter 3 were largely similar to those found by the Norwegian population-based study.[7]

*The interaction of PD with age*

Age was found to be an independent predictor of dementia in our study. This finding has been reported by several longitudinal studies and altogether this suggests an intrinsic relation between age and advancing disease which underlies the development of many late complications of PD.[8-11] Other symptoms that are mainly seen in older patients with advanced PD include autonomic dysfunction, PIGD, hallucinations and freezing.[12] Past studies showed that age also seems to interact with the severity of motor symptoms. In a prospective cohort study of non-demented PD cases, the combined effect of increasing age (>72 years) and severity of motor signs (median total Unified Parkinson's Disease Rating Scale motor score>24) was associated with a 10-fold risk of dementia, whereas the risk of dementia for PD patients with an age equal to or less than 72 years and motor signs (median total Unified Parkinson's Disease Rating Scale motor score>24) was not significantly elevated.[13]

In addition, we found that age also predicted a more persistent course of certain non-motor symptoms. For instance, in **chapter 6** we found that patients with persistent depression were often older at baseline (Table S6.1).

In fact, several studies suggested that age is an important modulating factor in the disease progression of PD. In an 8-year longitudinal study, patients who were older at onset had a more rapid decline in motor function, with an average annual decline of 2.6 points for those 50 years of age and 3.8 points for those who were 70.[14] Furthermore, a review on disease progression patterns of PD done by van Rooden et al. also showed that the disease profile of an older age-at-onset is associated with a more rapid disease progression.[15] Our study supports this finding and we found that a higher age-at-onset of PD indeed puts a patients more at risk to develop hallucinations (**chapter 2**).

*The role of gender in non-motor symptoms*

While PD in general seems to occur more frequently in men and at an earlier age in men,[16,17] we found that several non-motor symptoms of PD (hallucinations, depressive- and anxiety symptoms) occur more frequently in women. Earlier studies have already reported the association between female gender and depression/anxiety in PD, and it is a well-known phenomenon that females in the general population have a higher lifetime risk to develop depression or anxiety.[18,19] However, the higher risk for females to develop hallucinations has not been reported earlier and is a new finding. A potential explanation for this finding could be that female patients are more susceptible to develop side-effects of dopaminergic medication, which is supported by an earlier finding that female patients more often suffer from levodopa-induced dyskinesias.[20] This higher susceptibility for dopaminergic medication-induced side-effect in females is possibly due to the mediating effect of estrogen on the bioavailability of levodopa in the body.[21] This phenomenon could also explain why females have slower disease progression and milder motor deterioration in PD. According to an earlier single photon emission computed tomography (SPECT) study, this difference is probably due to a higher physiological striatal dopamine level in female PD patients.[22] There is also some evidence that other non-motor symptoms occur more frequently in males such as dementia and EDS.[8,10,23] In our study, we only confirmed this association for EDS, the higher risk for males to develop dementia was not found and some past longitudinal studies also did not find an association between male gender and dementia.[24,25] Altogether, our findings suggest that there is a clear role for gender in the development of some specific non-motor symptoms (EDS, depression and anxiety), while for other symptoms this relationship still needs to be confirmed by future studies (dementia and hallucinations).

*The role of dopamine agonists*

As mentioned earlier, non-motor symptoms have a significant impact on the quality of life in patients with PD. Antiparkinsonian agents are mainly targeted towards dopaminergic (motor) symptoms and often provide no benefit for non-motor symptoms, which are mainly of non-dopaminergic origin.[26] There is some evidence that dopamine agonists could improve depressive symptoms in PD, but this relationship was not consistently found.[27,28] Nevertheless, dopamine agonists could cause or even worsen other non-dopaminergic symptoms such as EDS,[29] hallucinations,[30] orthostatic hypotension[31] and impulse control disorders such as compulsive shopping or excessive gambling.[32,33] In our study, we found that higher doses of dopamine agonists is an independent predictor of EDS and insomnia. Dopamine agonists could have an impact on sleep in PD in different ways. Firstly, treatment with dopamine agonists increases the patients risk to develop visual hallucinations without insight, which in turn could cause nocturnal sleep disturbances such as sleep fragmentation,

vivid dreams/nightmares and acting out dreams.[34] Further, dopamine agonists have biphasic effects on sleep-wakefulness and this effect has been attributed to D2 receptor stimulation; at low doses they reduce wakefulness and enhance sleep, whereas at high doses they induce opposite effects.[35] The importance of dopamine agonist dose on the occurrence of a non-motor symptom is also illustrated by the study by Evans et al.,[36] who found that impulse control disorders are associated with an increased dopaminergic activation of the ventral striatum.[36]

In conclusion, while certain non-motor symptoms are inherent components of PD that increase in severity as the disease progresses, others are inarguably caused by antiparkinsonian medication. This also raises the question of whether the occurrence of certain non-motor symptoms such as EDS, hallucinations, insomnia and impulse-control disorders could be prevented, since these symptoms are mainly caused by antiparkinsonian medication. The answer is two-fold, on the one hand, identifying the patients at risk could prevent the development of certain medication-induced symptoms. In fact, the precaution of prescribing dopamine agonists for elderly patients with PD due to their increased risk to develop hallucinations is already applied in daily practice. On the other hand, there is some evidence that certain non-motor symptoms can occur in drug-naïve patients. For example, the Norwegian EDS study that was performed on 153 de novo PD patients found that 18 patients were already diagnosed with EDS at baseline (without any treatment), which highlights the multifactorial origin of EDS in PD.[7]

*Predominant nondopaminergic complex*

For several non-motor symptoms in our study (EDS, depression and anxiety), we found strong associations with a cluster of similar predictors. Interestingly, the same cluster of predictors were identified as part of a coherent predominantly non-dopaminergic (PND) symptom complex.[37] This symptom complex is present early in the disease course and worsens with disease progression, which likely is the consequence of progressive α-synuclein aggregate-related synaptopathy and axon degeneration of the nervous system.[38-40] The PND symptom complex consists of six nondopaminergic symptoms: cognitive impairment, depressive symptoms, EDS, psychotic symptoms, autonomic dysfunction, and PIGD. In the original publication on the PND complex, anxiety was not included in the analysis. Interestingly, however, our findings on predictors of anxiety in **chapter 7** suggest that this symptoms is yet another component of this complex. The symptoms of this complex largely do not improve on dopaminergic medication and might therefore be a better indicator of progressive underlying pathobiology of PD. In addition, other studies also suggest that specific nondopaminergic PD signs such as PIGD are more strongly associated with the development of dementia than traditional dopa-responsive signs such as rigidity.[41]

Collectively, the important role of predominantly non-dopaminergic symptoms along the course of the disease, highlight the need for efficacious medication which targets the fundamental pathobiology of PD.

**Future perspectives**

Non-motor symptoms in PD are common and have been increasingly recognized as an integral part of PD. New clinical diagnostic criteria have recently been published by the concerned Movement Disorders Task Force, which defines that at least one non-motor symptom should be present after a disease duration of five years.[42] The importance of non-motor symptoms in PD is also reflected in the recognition of a new stage of PD (prodromal PD), which is present before the onset of motor symptoms.[43] Prodromal PD is characterized by a predominant presence of non-motor symptoms which are related to the involvement of nondopaminergic structures of the brain and peripheral nervous system. Examples include EDS, constipation, impaired olfaction, depression and REM-sleep behavioural disorder (RBD).[43] Research into this prodromal stage of PD is rapidly expanding and could aid in the earlier identification of patients at risk to develop PD and help to select patients for potential neuroprotective therapy.

Another important lesson from this thesis is that certain non-motor symptoms are still poorly studied in a longitudinal design. While dementia in PD has been extensively evaluated in longitudinal studies, this is not the case for other non-motor symptoms such as EDS, insomnia, depression and anxiety. This may be explained by the more recent growing interest in role of other predominantly non-dopaminergic symptoms in PD. Therefore, most available research on predictors for non-motor symptoms in PD has been conducted in a cross-sectional design. In addition, past studies on this topic usually were underpowered. To identify risk factors with some degree of certainty, a considerable amount of patients must have developed an outcome of interest to obtain a solid notion of the robustness of the identified risk factors. Therefore, adequate cohort size (to prevent lack of power/type II error) and sufficient length of follow-up are important criteria in the design of longitudinal studies. Our study contributes to the existing knowledge regarding prognostic factors for disease progression patterns in PD, and important strengths of our study are related to the large cohort size, the long follow-up duration and the limited dropout. However, several important non-dopaminergic symptoms including impulse-control disorders, apathy, pain and freezing while “on” on dopaminergic medication, have not or scarcely been evaluated in longitudinal studies (our’s included), and require further attention.

While several associations that were found by earlier studies have now been confirmed longitudinally by analyses presented in this thesis, there are still several potentially

interesting baseline variables that have not been studied. Examples include RBD as a potential risk factor for developing psychosis or dementia, sleep-disordered breathing for EDS and pain for depression and so forth. However, the assessment of some of these symptoms, for example RBD is complicated. The minimal diagnostic criteria for RBD as defined by the revised International Classification of Sleep Disorders (ICSD) require electromyographic (EMG) evidence of maintained muscle tone in submental muscles or excessive activity in limb muscles during REM sleep, with one of the following: sleep-related injury or disruptive behaviour by history or abnormal sleep behaviours during REM sleep during polysomnography.[44] The complexity of criteria of RBD render its evaluation in a large prospective cohort difficult.

*Progression patterns and individualizing treatment in PD*

Growing evidence suggests that rate of progression is an important characteristic of subtypes in PD. Our study shows that a combination of demographic and disease-related factors are determinants for developing symptoms related to the PND complex, which likely is a solid clinical proxy of disease severity and progression. Additionally, patients may also differ with respect to how they respond the medication and their susceptibility to develop side-effects. Some patients experience adequate symptomatic control after many years on levodopa or dopamine agonists, while others experience a limited benefit of the treatment and develop more side-effects such as hallucinations and EDS. This individual variability in drug response could be caused by a genetic diversity in genes that code for enzymes involved in drug processing and drug receptor interaction.[45,46] Pharmacogenomics is a promising field that investigates which genetic markers are associated with differences in individual drug response. One possibility to address this is by examining which single nucleotide polymorphisms (SNPs) are associated with interindividual differences in metabolism, absorption, efficacy or side effects. A SNP is a DNA sequence variation occurring when a single nucleotide (A, T, C or G) in the genome differs between paired chromosomes in an individual. A genetic variation can be considered a 'SNP', when it occurs at a frequency of 1% or higher in a population.[47] Current research on 'pharmacogenetic' markers in PD has mainly focused on genes coding for processes involved in the metabolism of neurotransmitters that play a role in the pathogenesis of PD, such as dopamine receptors, dopamine transporters, monoamine oxidase A and B (MAO-A/B) and catechol-O-methyltransferase (COMT).[46] Differences between patients concerning their pharmacogenetics profile may explain the large variability between patient encountered in clinical practice on the level of effectiveness and toxicity of drugs. For example, there is some evidence that patients with the COMT Met/Met polymorphism are more at risk to develop dyskinesias, EDS and hallucinations.[49-51]

Our study shows that certain features of the clinical profile of PD are associated with an increased risk to develop a particular non-motor symptoms, e.g. EDS. Pharmacogenetic profiling may therefore be important in those patients who harbour these risk factors, since they are more prone to develop medication-induced symptoms. Knowledge from longitudinal studies does not only contribute to more insight in the underlying pathobiology of PD, but it could also help the caregiver to monitor patients with particular risk factors more closely and adjust treatment if necessary. In addition, more insight in these predictors could also contribute to a better identification of patients who benefit from potential disease-modifying or neuroprotective therapies. For the future, we hope to see more longitudinal data on the disease progression in PD from large cohorts, combined with a 'pharmacogenetic' profile of every patient. In this way, evidence-based medicine can make its transformation into 'personalized' medicine.

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Chapter 9:

# Samenvatting, conclusies en toekomstperspectieven

In dit proefschrift zijn longitudinale analyses beschreven die verricht zijn met de data uit het PROPARK-cohort, een cohort van 421 Parkinsonpatiënten die zijn gevolgd voor een duur van 5 jaar. Het voornaamste doel van dit proefschrift was om voorspellers en factoren te vinden die bijdragen aan de ontwikkeling van de zogenaamde niet-motorische symptomen van de Ziekte van Parkinson (ZvP). Sterke punten van onze studie waren de lange duur van follow-up, de uitgebreide klinische evaluatie van patiënten, de beperkte uitval van patiënten en de grootte van het cohort. De volgende niet-motorische symptomen zijn in dit proefschrift onderzocht: psychose (hallucinaties), dementie, slaperigheid overdag, slapeloosheid, depressie en angst.

**Hoofdstuk 1** is de introductie van het proefschrift en geeft een korte geschiedenis van de ziekte, het ziektebeloop en de uitdagingen in de huidige behandeling. Verder geeft het een korte introductie van de verschillende niet-motorische symptomen en de potentiële impact die ze kunnen hebben op de kwaliteit van leven van Parkinsonpatiënten.
In het tweede deel van het hoofdstuk worden de doelen beschreven van het onderzoek en wordt een overzicht gegeven van welke niet-motorische symptomen worden uitgelicht in het proefschrift. Verder wordt geïllustreerd dat het essentieel is om patiënten die een hoger risico hebben op een bepaald niet-motorisch symptoom te identificeren, zodat zorgverleners beter op deze symptomen kunnen anticiperen en ze beter kunnen herkennen. Daarnaast wordt een overzicht gegeven van de verschillende statistische methoden die in dit proefschrift worden gebruikt om voorspellers van niet-motorische symptomen te vinden. Het hoofdstuk wordt afgesloten met een kort overzicht van alle hoofdstukken, waarbij tevens bevindingen en tekortkomingen van eerdere studies over non-motorische symptomen worden besproken.

**Hoofdstuk 2** geeft een overzicht van de belangrijkste voorspellers voor het ontwikkelen van hallucinaties bij Parkinsonpatiënten. Eenentwintig procent van de patiënten in ons cohort had bij hun eerste bezoek last van hallucinaties, en zesenveertig procent van de patiënten ontwikkelde deze symptomen terwijl ze aanvankelijk hier geen last van hadden. We vonden dat hallucinaties werden veroorzaakt door een combinatie van risicofactoren die geassocieerd waren met een hogere leeftijd en ernstigere ziekte. Daarnaast vonden we dat een langere ziekteduur, depressieve en autonome symptomen, cognitieve disfunctie, slaapstoornissen en hogere doseringen levodopa geassocieerd waren met het ontwikkelen van hallucinaties. Deze bevindingen betekenen voor de kliniek dat patiënten met deze karakteristieken nauwkeuriger vervolgd moeten worden op het ontwikkelen van hallucinaties. Indien deze symptomen vóórkomen, zouden eventuele wijzigingen aan de Parkinsonmedicatie overwogen moeten worden om het ontwikkelen van een psychose te

voorkómen. De bevinding dat vrouwen een hogere kans hebben om hallucinaties te ontwikkelen bij Parkinson is nieuw en moet in toekomstige studies geverifieerd worden.

In **hoofdstuk 3** worden voorspellers van dementie bij Parkinson beschreven. Dementie komt veel voor bij deze ziekte en is zeer invaliderend. Sommige longitudinale studies laten een prevalentie zien van 80-100% bij patiënten die tot 20 jaar zijn gevolgd.[1] In ons cohort had tweeëndertig procent van de patiënten dementie bij de eerste meting, terwijl zesentwintig procent van de niet-demente patiënten alsnog dementie ontwikkelde gedurende de vijf jaar follow-up. De bevindingen voor dementie kwamen grotendeels overeen met onze bevindingen bij hallucinaties; we vonden namelijk dat ook dementie werd veroorzaakt door een combinatie van risicofactoren die geassocieerd zijn met een hogere leeftijd en ernstigere ziekte. Motorische symptomen zoals houdings- en balansstoornissen, dyskinesieën, en non-dopaminerge symptomen zoals autonome disfunctie, slaperigheid overdag, hallucinaties en depressie verhogen allemaal de kans voor Parkinsonpatiënten om dementie te krijgen.

In **hoofdstuk 4** worden het beloop, de cross-sectionele en longitudinale associaties, en de risicofactoren van overmatige slaperigheid overdag bij Parkinsonpatiënten beschreven. In ons cohort was er een prevalentie van overmatige slaperigheid overdag van 43% op het eerste meetmoment, terwijl 46% van de patiënten zonder slaperigheid op baseline dit symptoom ontwikkelde tijdens de follow-up. Verder vonden we dat slaperigheid overdag een niet-persisterend symptoom was, maar naarmate patiënten langer werden gevolgd, nam de persistentie van het symptoom toe. Het mannelijk geslacht, slapeloosheid ’s nachts, cognitieve en autonome disfunctie, hallucinaties, minder ernstige dyskinesieën, een hogere dosering van dopamineagonisten en het gebruik van bloeddrukverlagende middelen waren allen geassocieerd met ernstigere symptomen van slaperigheid overdag over tijd. Voor patiënten die geen slaperigheid hadden op baseline, waren hogere scores voor slaperigheid op baseline en een ziektebeeld gedomineerd door houdings- en balansstoornissen voorspellers voor het krijgen van slaperigheid overdag in de toekomst. Sommige risicofactoren voor slaperigheid overdag, zoals de dosering van dopamineagonisten en het gebruik van bloeddrukverlagende middelen, kunnen eventueel aangepast worden, en patiënten met deze risicofactoren moeten nauwkeurig gemonitord worden om hun kwaliteit van leven te bewaken

**In hoofdstuk 5** ligt de focus op het beloop van en de factoren die geassocieerd zijn met longitudinale veranderingen in slaapklachten ’s nachts bij Parkinson. Slapeloosheid is een invaliderend symptoom bij de ziekte van Parkinson dat weinig is onderzocht in een

longitudinale opzet. Kennis over de risicofactoren die geassocieerd zijn met het vóórkomen van slapeloosheid kan aanknopingspunten bieden om de onderliggende ziektemechanismen van dit symptoom te begrijpen en om het symptoom eerder op te sporen. Een 'linear mixed model' (LMM) analyse werd gebruikt om factoren te identificeren die samenhangen met longitudinale veranderingen van de ernst van slapeloosheid over tijd en 'generalized estimating equations' (GEE) analyses werden uitgevoerd om vast te stellen welke baselinevariabelen geassocieerd waren met de verschillende aspecten van slapeloosheid (problemen met het in slaap vallen of een frequente onderbreking van de slaap). In ons cohort waren 'SCOPA-SLEEP-Nighttime Sleep' (NS) scores, een maat om de ernst van de nachtelijke slaapklachten te meten, beschikbaar voor 412 patiënten op baseline, waarvan 110 (27%) al slapeloosheid ('SCOPA-SLEEP-NS score' ≥ 7) hadden. Van de resterende 302 patiënten, ontwikkelden 99 (33%) slapeloosheid gedurende de follow-up. We vonden dat ernstigere depressieve symptomen, motorische fluctuaties, hogere doseringen van dopamineagonisten en het gebruik van slaapmiddelen onafhankelijk geassocieerd waren met meer slapeloosheidsymptomen over tijd. Aan de hand van de GEE analyse werd geen unieke set van determinanten gevonden die een specifiek aspect van slapeloosheid beïnvloedde.

Het doel van **hoofdstuk 6** is om associaties en voorspellers te vinden voor depressie bij Parkinsonpatiënten. Depressie is een veelvoorkomend niet-motorisch symptoom bij de ziekte van Parkinson. Verschillende eerdere studies hebben gevonden dat depressie de belangrijkste determinant is voor een slechte kwaliteit van leven bij Parkinson.[2,3] Het diagnosticeren van depressie bij patiënten met de ziekte van Parkinson wordt bemoeilijkt vanwege een overlap van de symptomen gerelateerd aan depressie met de symptomen die primair onderliggend zijn aan Parkinson zelf (bv. maskergelaat, traagheid van bewegen, moeheid, gewichtsverandering, concentratieverlies, overmatige slaperigheid of slapeloosheid).[4] Meer kennis over associaties en voorspellers van depressie bij de ziekte van Parkinson kan de vroege opsporing ervan mogelijk maken en een basis leggen voor toekomstige interventies. Wij vonden in ons cohort dat de proportie van patiënten met depressie ongeveer 20% was en dat dit percentage min of meer gelijk bleef gedurende de follow-up. Bij de helft van deze gevallen was depressie persistent. Vrouwelijk geslacht, ernstigere beperkingen in de dagelijkse activiteiten, ernstigere motorische fluctuaties, autonome en cognitieve disfunctie, slapeloosheid 's nachts en slaperigheid overdag waren onafhankelijk geassocieerd met meer depressieve symptomen over tijd. Verder waren meer depressieve symptomen op baseline, slaperigheid overdag en een hogere dosering levodopa onafhankelijke voorspellers voor het krijgen van depressie bij de patiënten die geen depressie hadden op baseline. Uit deze bevindingen kunnen we concluderen dat,

afgezien van motorische fluctuaties en de dosering van levodopa, depressieve symptomen bij de ziekte van Parkinson voornamelijk gerelateerd zijn aan factoren van non-dopaminerge origine. Dit suggereert ook dat depressie bij Parkinson een gevolg is van de progressie van de pathobiologie van de ziekte, wat ook verklaart waarom de huidige behandeling van deze symptomen in de praktijk moeilijk is.

Het doel van het onderzoek in **hoofdstuk 7** is om te evalueren welke kenmerken geassocieerd zijn met de longitudinale veranderingen in angst bij Parkinson. Een recente review heeft een gemiddelde prevalentie van angststoornissen gevonden van 31% bij Parkinsonpatiënten.[5] Daarmee is het een frequent voorkomend symptoom dat tevens een belangrijke invloed uitoefent op de kwaliteit van leven. Er is echter weinig bekend over welke risicofactoren een rol spelen bij het ontwikkelen van angstsymptomen bij Parkinson. In deze studie werd LMM gebruikt om factoren te identificeren die samenhangen met longitudinale veranderingen in de 'Hospital Anxiety and Depression – Anxiety' (HADS-A) scores. Verder werd een 'survival analysis' uitgevoerd met de data van patiënten die op baseline niet angstig waren, teneinde voorspellers voor het ontwikkelen van angst (oftewel HADS-A≥11) in deze groep patiënten te identificeren.
Van de 409 patiënten van wie een HADS-A score beschikbaar was op baseline, hadden 67 (16%) al angstsymptomen op dat moment, terwijl 64 (19%) van de overige 342 niet-angstige patiënten angstsymptomen ontwikkelden na een gemiddelde follow-up duur van 2,6 jaar. Zeventig procent van de patiënten met angst waren ook depressief. Vrouwelijk geslacht, cognitieve disfunctie, depressieve symptomen, autonome disfunctie, slapeloosheid 's nachts en slaperigheid overdag waren alle geassocieerd met meer angstsymptomen over tijd. Afgezien van vrouwelijke geslacht en slaperigheid overdag, waren alle variabelen ook onafhankelijke voorspellers voor het ontwikkelen van angst bij patiënten die op baseline niet angstig waren. Onze bevindingen suggereren dat het ontstaan van angst bij Parkinson geassocieerd is met vrouwelijke geslacht, cognitieve beperkingen, autonome disfunctie, slapeloosheid 's nachts en slaperigheid overdag. Daarnaast zijn angst en depressie vaak tegelijkertijd aanwezig bij de Parkinsonpatiënten en delen ze dezelfde onderliggende risicofactoren, hetgeen mogelijk wijst op een gedeeld pathofysiologisch verband tussen de twee symptomen.

Een overzicht van de belangrijkste longitudinale verbanden en risicofactoren die zijn beschreven in dit proefschrift wordt weergegeven in Tabel 9.1.

**Tabel 9.1:** Overzicht van variabelen die longitudinaal geassocieerd zijn met niet-motorische symptomen bij de Ziekte van Parkinson*

| Uitkomstmaat | Variabelen uit de survival analysis[a] | Variabelen uit de LMM[b] |
|---|---|---|
| Hallucinaties[c] | Vrouwelijk geslacht<br>↑ Leeftijd begin symptomen<br>Dyskinesieën<br>Slaperigheid overdag<br>Autonome disfunctie | Vrouwelijk geslacht<br>↑ Leeftijd begin symptomen<br>Dyskinesieën<br>Slaperigheid overdag<br>Autonome disfunctie |
| Dementie[d] | ↑ Leeftijd<br>↓ Opleiding<br>Slaperigheid overdag<br>↑ Levodopa dosering | ↑ Leeftijd<br>↓ Opleiding<br>Slaperigheid overdag<br>Houdings- en balansstoornissen<br>↑ Levodopa dosering |
| Slaperigheid overdag | Ernst slaperigheid overdag op baseline<br>Houdings- en balansstoornissen<br>Autonome disfunctie (UR)<br>Bloeddrukverlagende medicatie | Mannelijk geslacht<br>↓ Dyskinesieën<br>Cognitieve beperking<br>Hallucinaties<br>Slapeloosheid 's nachts<br>Autonome disfunctie (UR, GI)<br>↑ dosering dopamine agonisten<br>Bloeddrukverlagende medicatie<br>Geen gebruik van benzodiazepines |
| Slapeloosheid 's nachts[e] | Depressieve symptomen | Motorische fluctuaties<br>Depressieve symptomen<br>↑ dosering dopamine agonisten<br>Gebruik van slaapmedicatie |
| Depressie | Ernst depressieve symptomen op baseline<br>Slaperigheid overdag<br>↑ Levodopa dosering | Vrouwelijk geslacht<br>ADL beperkingen<br>Motorische fluctuaties<br>Cognitieve beperking<br>Slapeloosheid 's nachts<br>Slaperigheid overdag<br>Autonome disfunctie (CV,UR)<br>Gebruik van antidepressiva |
| Angst | Cognitieve beperking<br>Slapeloosheid 's nachts<br>Autonome disfunctie (CV) | Vrouwelijk geslacht<br>Cognitieve beperking<br>Slapeloosheid 's nachts<br>Slaperigheid overdag<br>Autonome disfunctie (GI, CV)<br>Gebruik van antidepressiva<br>Gebruik van benzodiazepines |

*Afkortingen: LMM, linear mixed models; UR, urogenitaal; GI, gastro-intestinaal; CV, cardiovasculair; ADL, activiteiten van het dagelijkse leven*

**Alle variabelen zijn van boven naar beneden weergegeven in afnemende sterkte van het verband tussen desbetreffende variabele en de uitkomst.*

*[a] Dit beantwoordt de vraag **w**elke factoren geassocieerd zijn met een verhoogd risico om een bepaald symptoom te ontwikkelen bij patiënten die het symptoom niet hebben op baseline.*

*[b] Dit beantwoordt de vraag welke factoren geassocieerd zijn met longitudinale veranderingen in de ernst van een bepaald symptoom.*

*[c] In het oorspronkelijke manuscript (Hoofdstuk 2) werd geen LMM analyse gedaan; LMM analyse leverde dezelfde resultaten op als de survival analyse.*

*[d] In de oorspronkelijke analyse zoals beschreven in hoofdstuk 3 werd geen LMM gedaan. De LMM analyse leverde dezelfde resultaten op als de survival analyse, behalve dat houdings- en balansstoornissen een nieuwe bevinding was.*

*[e] Survival analyse niet beschreven in de oorspronkelijke publicatie. Na het uitvoeren van de survival analyse, waren alleen depressieve symptomen significant geassocieerd met nachtelijke slaapklachten.*

**Afsluitende opmerkingen**

Dit proefschrift is gebaseerd op analyses van de data uit een groot longitudinaal cohort van 421 patiënten met de ziekte van Parkinson, die gevolgd zijn over een periode van vijf jaar. 'Survival analysis' en 'linear mixed models (LMM)' werden toegepast om voorspellers te identificeren die het vóórkomen van bepaalde niet-motorische symptomen konden voorspellen. In essentie probeerden we antwoorden te vinden op twee vragen, namelijk "Welke factoren zijn geassocieerd met longitudinale veranderingen in de ernst van een bepaald symptoom?"(LMM) en "Welke factoren zijn geassocieerd met een verhoogd risico om een bepaald symptoom te ontwikkelen bij patiënten die dit symptoom niet hebben op baseline?" ('survival analysis'). De eerste methode (LMM) geeft een completere kijk op de factoren die geassocieerd zijn met de variatie van een bepaald symptoom over tijd. De belangrijkste voordelen van deze methode is dat we de data van alle patiënten in ons cohort kunnen gebruiken en dat het kan omgaan met missende waarden in de uitkomsten. De tweede methode (survival) is voornamelijk interessant vanuit een klinisch oogpunt, omdat het inzicht geeft in de factoren vindt die verantwoordelijk zijn voor de ontwikkeling van een bepaald symptoom bij patiënten die dat symptoom aanvankelijk nog niet hadden. Een potentieel nadeel van deze methode is dat een afkappunt gebruikt moet worden om patiënten te classificeren. Het gebruik van een afkappunt heeft een risico op misclassificatie (over- of onderschatting van potentiële voorspellers), omdat individuele scores van patiënten rondom het afkappunt kunnen schommelen.

Aan het begin van dit project lag de focus op survival analysis. Omdat survival analyse en LMM echter complementair zijn en in combinatie een overzichtelijker en completer beeld schetsen van het longitudinale beloop van het desbetreffend symptoom, werd later besloten beide analyses te combineren. Aanvankelijk werd dus de LMM methode niet toegepast in de oorspronkelijke publicaties van hoofdstuk 2 (hallucinaties) en hoofdstuk 3 (dementie). Echter, na het toepassen van de LMM in een later stadium vonden we nagenoeg dezelfde resultaten voor deze symptomen als welke bij de survival analyse gevonden werden. Deze bevindingen tonen dan ook aan dat onze oorspronkelijke bevindingen robuust waren. Het gebruikmaken van een afkappunt leidde ook tot lagere prevalentiewaarden voor angst en depressie in onze studie. Dit verschil kan ook verklaard worden door het feit dat andere studies andere meetmethoden hadden gebruikt om beide symptomen te evalueren. Voor angst bijvoorbeeld, hadden sommige studies criteria gebruikt uit het 'Diagnostic Manual for Mental Disorders' (DSM) om patiënten te classificeren.[6] Hoewel dit een preciezere manier is om een angststoornis te diagnosticeren, en ook de potentie heeft om een specifieke subcategorie van angststoornis te identificeren (bv. sociale fobie, paniekstoornis), geeft het echter geen informatie over de ernst van de angstsymptomen. Een andere verklaring voor

een lagere prevalentie voor angst in onze studie kan het gebruik zijn van een meer conservatief afkappunt (10/11, waarschijnlijke angststoornis) in plaats van het afkappunt 7/8 (mogelijke angststoornis). Dit kon leiden tot een onderschatting van het werkelijke prevalentiecijfer voor angst in onze studie.

Voor het interpreteren van de resultaten van onze analyses is het belangrijk om rekening te houden met de opbouw van de studiepopulatie. In dit proefschrift is het cohort gebaseerd op Parkinsonpatiënten uit een ziekenhuispopulatie en niet op die van de algemene populatie. Daarnaast hebben we een prestratificatiestrategie toegepast, welke is gebaseerd op de beginleeftijd van de Parkinsonsymptomen en de ziekteduur. Deze strategie kan invloed gehad hebben op de prevalentie en op de ernst van bepaalde symptomen, en daarmee ook op de generaliseerbaarheid van de bevindingen. Echter, het doel van deze studie was niet om incidentieproporties te berekenen van bepaalde niet-motorische symptomen, maar om voorspellers te vinden voor het ontwikkelen van deze symptomen. We kunnen daarom niet uitsluiten dat de verhoogde variatie in beginleeftijd en ziekteduur als gevolg van de stratificatiestrategie van invloed is geweest op de sterkte van de gevonden verbanden, maar het is niet waarschijnlijk dat er een zodanige vertekening in significantie en richting van de gevonden verbanden heeft plaatsgevonden dat de gevonden bevindingen niet generaliseerbaar zouden zijn naar andere ziektepopulaties. Bijvoorbeeld, de voorspellers die we gevonden hebben voor slaperigheid overdag in hoofdstuk 3 kwamen grotendeels overeen met de voorspellers die eerder gevonden waren in een studie uit Noorwegen, die uitgevoerd was in een patiëntengroep afkomstig uit de algemene populatie.

*De interactie van Parkinson met leeftijd*

Leeftijd was in onze studie een onafhankelijke voorspeller van dementie. Deze bevinding is eerder gerapporteerd in meerdere longitudinale studies en suggereert een intrinsieke relatie tussen leeftijd en de voortschrijdende ziekte die mogelijk ten grondslag ligt aan de ontwikkeling van meerdere late complicaties van Parkinson. [8-11] Andere symptomen die met name bij oudere patiënten met een gevorderde ziekte vóórkomen zijn onder andere autonome disfunctie, houdings- en balansstoornissen, hallucinaties en 'freezing'.[12] Eerdere studies hebben ook gevonden dat leeftijd en de ernst van motorische symptomen een interactie hebben met elkaar. In een prospectief cohortonderzoek bij niet-demente Parkinsonpatiënten was het gecombineerde effect van toenemende leeftijd (>72 jaar) en de ernst van motorische symptomen (mediaan van totale 'Unified Parkinson's Disease Rating Scale motor score' (UPDRS) >24) geassocieerd met een tienvoudig verhoogd risico om dementie te ontwikkelen, terwijl het risico op dementie voor patiënten met een leeftijd gelijk

aan of lager dan 72 jaar en een hogere ernst van motorische symptomen (mediaan totale UPDRS motor score>24) dit risico niet significant verhoogd was.[13]
Verder vonden we dat leeftijd ook een voorspeller was voor een meer persisterend beloop van bepaalde niet-motorische symptomen. Bijvoorbeeld, in **hoofdstuk 6** vonden we dat patiënten met een persisterende depressie vaak ouder waren op baseline (Tabel S6.1). Diverse eerdere studies hebben in feite gesuggereerd dat leeftijd een belangrijke modulerende factor is voor de ziekteprogressie van Parkinson. In een 8-jarige longitudinale studie vertoonden patiënten die ouder waren bij het begin van de symptomen een sterkere achteruitgang van motorische functie, met een gemiddelde jaarlijkse afname van 2.6 punten op de UPDRS schaal bij 50 jaar en 3.8 punten voor degenen die symptomen kregen bij 70 jaar.[14] Daarnaast is uit een review over patronen van ziekteprogressie bij Parkinson door van Rooden en collega's gebleken dat een hogere beginleeftijd van symptomen geassocieerd is met een snellere ziekteprogressie.[15] Onze studie ondersteunt deze bevinding en we vonden dat een patiënt met een hogere beginleeftijd van symptomen inderdaad een hoger risico heeft op het ontwikkelen van hallucinaties (**hoofdstuk 2**).

*De rol van geslacht bij niet-motorische symptomen*
De ziekte van Parkinson (ZvP) komt in de algemene bevolking vaker voor bij mannen en begint bij hen ook op een jongere leeftijd.[16,17] Echter, in onze studie vonden we dat sommige niet-motorische symptomen van Parkinson juist vaker voor kwamen bij vrouwen (hallucinaties, depressie- en angstsymptomen). Eerder hebben studies al een associatie gevonden tussen vrouwelijk geslacht en depressie/angst bij Parkinsonpatiënten, en het is een bekend fenomeen dat vrouwen in de algemene populatie ook een hoger risico hebben om een depressie of angststoornis te ontwikkelen.[18,19] Echter, een hoger risico voor vrouwen om hallucinaties te ontwikkelen bij Parkinson is een nieuwe bevinding. Een potentiële verklaring hiervoor is dat vrouwen gevoeliger zijn voor het ontwikkelen van bijwerkingen op dopaminerge medicatie. Dit wordt ondersteund door een eerdere bevinding dat vrouwelijke Parkinsonpatiënten vaker last hebben van levodopa-geïnduceerde dyskinesieën.[20] De hogere gevoeligheid voor deze medicatie-geïnduceerde bijwerkingen bij vrouwen komt mogelijk door het effect van oestrogeen op de biologische beschikbaarheid van levodopa in het lichaam.[21] Dit fenomeen kan ook verklaren waarom vrouwen een tragere ziekteprogressie en een mildere motorische achteruitgang hebben. In een eerdere 'single photon emission computed tomography' (SPECT) studie wordt dit verschil verklaard door hogere fysiologische dopaminespiegels in het striatum van vrouwelijke Parkinsonpatiënten.[22] Er zijn tevens aanwijzingen dat andere niet-motorische symptomen juist vaker vóórkomen bij mannen, zoals dementie en slaperigheid overdag.[8,10,23] In onze studie hebben we dit verband alleen gevonden voor slaperigheid overdag; het hogere risico voor mannen om

dementie te ontwikkelen hebben we niet gevonden en er zijn eerdere studies die dit verband ook niet vonden in hun studie. [24,25] Samenvattend, onze bevindingen suggereren dat er een duidelijke rol is van geslacht in de ontwikkeling van sommige specifieke niet-motorische symptomen (slaperigheid overdag, depressie en angst), terwijl voor andere symptomen dit verband nog nader geverifieerd moet worden in toekomstige studies (dementie en hallucinaties).

*De rol van dopamineagonisten*

Niet-motorische symptomen hebben een significante impact op de kwaliteit van leven van Parkinsonpatiënten. Parkinsonmedicatie is met name gericht op dopaminerge (motorische) symptomen en heeft meestal weinig effect op niet-motorische symptomen, die met name van non-dopaminerge origine zijn.[26] Er is enig bewijs dat dopamineagonisten depressieve symptomen kunnen verbeteren bij Parkinsonpatiënten, maar in andere studies wordt dit effect niet consistent gevonden. [27,28]

Desalniettemin kunnen dopamineagonisten juist bepaalde non-dopaminerge symptomen veroorzaken of zelfs verergeren, zoals slaperigheid overdag,[29] hallucinaties,[30] orthostatische hypotensie[31] en impulscontrolestoornissen waaronder overmatig shoppen of gokken.[32,33] In onze studie vonden we dat een hogere dosering dopamineagonisten een onafhankelijke voorspeller is van slaperigheid overdag en slapeloosheid ’s nachts. Dopamineagonisten kunnen op verschillende manieren een invloed hebben op slaap bij Parkinson. Ten eerste hebben patiënten die behandeld worden met dopamineagonisten een hoger risico op het ontwikkelen van visuele hallucinaties zonder (behoud van) inzicht, dat op haar beurt weer kan leiden tot nachtelijke slaapstoornissen, zoals onderbreking van de slaap, levendige dromen/nachtmerries en het uitleven van dromen.[34] Daarnaast hebben dopamineagonisten een bifasisch effect op het slaap-waakritme en dit effect wordt toegeschreven aan de stimulatie van D2 receptoren; bij lage doseringen verminderen ze de waakzaamheid en verbeteren ze de slaap, terwijl bij hoge doseringen ze juist het tegenovergestelde effect kunnen induceren.[35] De betekenis van de dosering van dopamineagonisten op het vóórkomen van een niet-motorisch symptoom wordt ook geïllustreerd door een studie die is verricht door Evans en collega’s[36] die vonden dat impulscontrolestoornissen geassocieerd zijn met een toegenomen dopaminerge activatie van het ventrale striatum.[36]

Uit het bovenstaande kunnen we concluderen dat bepaalde niet-motorische symptomen inherente componenten zijn van de onderliggende ziekte, die in ernst toenemen naarmate de ziekte progressie toont, terwijl andere voornamelijk veroorzaakt worden door Parkinsonmedicatie. Hierbij kan men zich afvragen of bepaalde niet-motorische symptomen voorkómen kunnen worden, gezien de rol van Parkinsonmedicatie bij sommige symptomen. Het antwoord op deze vraag kan op twee manieren gegeven worden. Ten eerste is het zo

dat het wel degelijk mogelijk is om patiënten die een verhoogd risico lopen op medicatiegeïnduceerde symptomen te identificeren; sterker nog, de voorzichtigheid bij het voorschrijven van dopamineagonisten bij oudere patiënten wordt al in de dagelijkse praktijk toegepast wegens het hogere risico op het ontwikkelen van hallucinaties. Echter, er is ook bewijs dat bepaalde niet-motorische symptomen vóórkomen bij Parkinsonpatiënten die nog nooit zijn behandeld met Parkinsonmedicatie. Bijvoorbeeld in een studie naar slaperigheid overdag uit Noorwegen, die uitgevoerd werd bij 153 de-novo-Parkinsonpatiënten, vonden de auteurs dat 18 patiënten al slaperigheid overdag hadden bij het eerste bezoek, dus zonder dat zij enige behandeling hadden ondergaan. Deze bevinding benadrukt ook dat slaperigheid overdag bij Parkinson een multifactoriële origine heeft.[7]

*Predominant non-dopaminergic complex*

Voor verscheidene niet-motorische symptomen in onze studie (slaperigheid overdag, depressie en angst), vonden we sterke associaties met een cluster van min of meer gelijke predictoren. Het opmerkelijke is dat hetzelfde cluster van voorspellers ook eerder geïdentificeerd was als een onderdeel van een coherent non-dopaminerg symptoomcomplex (PND).[37] Dit complex van symptomen is al vroeg gedurende het ziektebeloop aanwezig en verergert naarmate de ziekte voortduurt, wat zeer waarschijnlijk een gevolg is van progressieve, aan α-synucleïneaggregatie gerelateerde synaptopathie en axonale degeneratie van het zenuwstelsel.[38-40] Het PND-complex bestaat uit zes non-dopaminerge symptomen: cognitieve disfunctie, depressieve symptomen, slaperigheid overdag, psychose, autonome disfunctie en houdings- en balansstoornissen. In de oorspronkelijke publicatie waar dit complex voor het eerst werd beschreven, werd angst niet opgenomen in de analyse. Opmerkelijk is dat onze bevindingen over de voorspellers van angst in **hoofdstuk 7** suggereren dat dit symptoom ook deel uitmaakt van het complex. De symptomen van dit complex verbeteren niet met het gebruik van dopaminerge medicatie en zijn dus goede indicatoren van de onderliggende progressieve pathobiologie van Parkinson. Verder suggereren ook andere studies dat specifieke non-dopaminerge symptomen zoals houdings- en balansstoornissen sterker geassocieerd zijn met het ontwikkelen van dementie dan de klassieke voor levodopa gevoelige symptomen zoals rigiditeit.[41]

Allesomvattend kunnen we concluderen dat er een belangrijke rol is van de non-dopaminerge symptomen met betrekking tot het beloop van de ziekte; dit benadrukt ook de behoefte aan effectieve medicatie die op de fundamentele pathobiologie van Parkinson aangrijpt.

**Toekomstperspectieven**

Niet-motorische symptomen van de ziekte van Parkinson zijn veelvoorkomend en worden in toenemende mate herkend als een integraal onderdeel van de ziekte. Nieuwe diagnostische criteria zijn daarom recent gepubliceerd door de 'task force' van de internationale vereniging van bewegingsstoornissen ('Movement Disorders Society'). Zij definiëren namelijk dat voor de diagnose van de ziekte van Parkinson minimaal één niet-motorisch symptoom aanwezig moet zijn na een ziekteduur van vijf jaar.[42]

Het belang van niet-motorische symptomen bij Parkinson wordt ook teruggevonden in de erkenning van een nieuw stadium van Parkinson ('prodromal PD'), een stadium dat aanwezig is vóór het begin van motorische symptomen.[43] 'Prodromal PD' wordt voornamelijk gekarakteriseerd door de aanwezigheid van niet-motorische symptomen die samenhangen met schade aan de non-dopaminerge structuren van het centrale en perifere zenuwstelsel. Voorbeelden zijn slaperigheid overdag, obstipatie, reukverlies, depressie en 'REM-sleep behavioural disorder' (RBD).[43] Onderzoek naar dit voorstadium van Parkinson breidt zich momenteel snel uit en kan een belangrijke bijdrage leveren in het eerder opsporen van patiënten die een hoger risico lopen om Parkinson te ontwikkelen. Daarnaast helpt het ook om patiënten te selecteren voor potentiële neuroprotectieve therapie.

Een andere belangrijke les uit dit proefschrift is dat bepaalde niet-motorische symptomen nog steeds slecht zijn onderzocht in longitudinaal verband. Sommige symptomen zoals dementie zijn uitgebreid onderzocht in voormalige longitudinale studies, terwijl voor andere niet-motorische symptomen, zoals slaperigheid overdag, slapeloosheid, depressie en angst dat niet het geval is. Dit kan verklaard worden door de pas recent groeiende interesse in de rol van andere non-dopaminerge symptomen bij Parkinson. Daarom zijn de beschikbare studies over deze onderwerpen met name cross-sectioneel opgezet. Verder hebben eerdere studies over deze onderwerpen vaak een lage power. Om met een bepaalde graad van zekerheid risicofactoren te kunnen vinden, moet men er voor zorg dragen dat een aanzienlijke hoeveelheid patiënten de uitkomst waarin men geïnteresseerd is zal ontwikkelen, zodat er een betrouwbare indruk bestaat over de eventueel gevonden risicofactoren. Daarom zijn de grootte van het cohort (voorkómen van een lage power/type II fout) en de follow-up duur belangrijke criteria voor het opzetten van longitudinale onderzoeken.

Onze studie levert een bijdrage aan de bestaande kennis over welke prognostische factoren de progressie(patronen) van Parkinson beïnvloeden. Sterke punten van onze studies zijn met name de grootte van het cohort, de lange follow-upduur en de beperkte uitval van patiënten. Echter, er zijn nog andere belangrijke non-dopaminerge symptomen, zoals impulscontrolestoornissen, apathie, pijn en freezing tijdens gebruik van dopaminerge

medicatie, die niet of nauwelijks zijn bestudeerd in longitudinale studies (inclusief onze studie).
Meerdere associaties die in eerdere studies zijn gevonden zijn door onze studie in longitudinaal verband bevestigd. Er zijn echter nog andere potentiële baselinevariabelen die niet in onze studie zijn opgenomen, maar wel interessant kunnen zijn. Voorbeelden zijn: RBD als een risicofactor voor het ontwikkelen van psychose of dementie, slaapgerelateerde ademhalingsproblemen als voorspeller voor slaperigheid overdag, pijn als voorspeller voor depressie enzovoort. De evaluatie van sommige van deze symptomen, bijvoorbeeld RBD, kan echter gecompliceerd zijn. De minimale diagnostische criteria voor RBD zoals gedefinieerd in de gereviseerde International Classification of Sleep Disorders (ICSD) stelt dat er elektromyografisch bewijs moet zijn van een behouden spiertonus in de submentale spieren of overmatige activiteit in de ledematen tijdens de REM-slaap, met daarnaast minstens één van de volgende ondersteunende verschijnselen voor de diagnose: slaapgerelateerde verwondingen, anamnestisch slaapverstorend gedrag of abnormale gedragingen tijdens de REM-slaap gedurende een polysomnografie.[44] De complexiteit van deze RBD-criteria maakt het evalueren ervan in een groot prospectief cohort moeilijk.

*Progressiepatronen en het individualiseren van de behandeling*
Er is steeds meer bewijs dat de mate van progressie een belangrijk kenmerk is van de verschillende subtypes van Parkinson. Onze studie laat zien dat een combinatie van demografische en ziektegerelateerde factoren determinanten kunnen zijn voor symptomen die gerelateerd zijn aan het eerdergenoemde PND-complex, dat waarschijnlijk een klinische maat is voor ziekte-ernst en progressie. Daarnaast kunnen patiënten ook verschillen in de mate waarin ze reageren op de medicatie en in hun gevoeligheid om bepaalde bijwerkingen te ontwikkelen. Sommige patiënten ervaren een goede controle van hun symptomen na vele jaren behandeling met levodopa of dopamineagonisten, terwijl anderen een beperkte verbetering ondervinden na behandeling en meer bijwerkingen ontwikkelen, zoals hallucinaties of slaperigheid overdag. Deze individuele variatie in respons op medicatie kan veroorzaakt worden door een diversiteit in de genen die coderen voor enzymen die betrokken zijn bij het metabolisme van medicatie en de interactie van deze medicatie en diens aangrijpingspunt.[45,46] Farmacogenetica is een veelbelovend onderzoeksgebied dat onderzoekt welke genetische markers geassocieerd zijn met verschillen in individuele medicatierespons. Eén mogelijkheid om dit te onderzoeken is door na te gaan welke ‘single nucleotide polymorphisms’ (SNPs) geassocieerd zijn met individuele verschillen in metabolisme, opname, effectiviteit of bijwerkingen. Een SNP is een variatie die ontstaat op één stuk DNA wanneer een nucleotide (A, T, C of G) in het genoom verschilt tussen gepaarde chromosomen van één individu. Een genetische variatie wordt gezien als een

‘SNP’ als het met een frequentie van 1% of hoger in een populatie vóórkomt.[47] Huidig onderzoek naar farmacogenetische markers is met name gefocust op genen die coderen voor processen die betrokken zijn bij het metabolisme van neurotransmitters die een rol spelen bij de pathogenese van Parkinson, zoals dopaminereceptoren, dopaminetransporters, monoamineoxidase A en B (MAO-A/B) en catechol-O-methyltransferase (COMT).[46] Verschillen in farmacogenetisch profiel tussen patiënten kunnen de grote variabiliteit tussen patiënten met betrekking tot de effectiviteit en toxiciteit van hun medicatie in de klinische praktijk verklaren. Zo is er bijvoorbeeld bewijs dat patiënten met het Met/Met-polymorfisme in het COMT-gen een hogere kans hebben op het ontwikkelen van dyskinesieën, slaperigheid overdag en hallucinaties.[49-51]
Onze studie laat zien dat bepaalde eigenschappen van het klinisch profiel van Parkinson geassocieerd zijn met een hoger risico op het ontwikkelen van bepaalde niet-motorische symptomen, bijvoorbeeld slaperigheid overdag. Farmacogenetisch profileren kan dus met name belangrijk zijn bij patiënten die deze risicofactoren hebben, omdat ze meer risico lopen om deze medicatiegeïnduceerde symptomen te ontwikkelen. Kennis uit longitudinale onderzoeken leveren niet alleen bijdrage aan meer inzicht in de onderliggende pathofysiologie van Parkinson, maar het helpt ook de zorgverlener om de patiënten die bepaalde risicofactoren hebben beter te monitoren en indien nodig hun behandeling aan te passen. Verder helpt meer inzicht in deze risicofactoren ook bij het opsporen van patiënten die baat kunnen hebben bij potentiële ziekteremmende of neuroprotectieve therapieën. In de toekomst zien we graag meer onderzoeken naar de ziekteprogressie bij Parkinson die zijn gebaseerd op grote longitudinale cohorten, gecombineerd met een ‘farmacogenetisch’ profiel van iedere patiënt. Op deze manier kan evidence-based medicine een transformatie maken naar ‘personalized’ medicine.

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# List of Publications

1. Risk factors for hallucinations in Parkinson's disease: results from a large prospective cohort study. Zhu K, van Hilten JJ, Putter H, Marinus J. *Movement Disorders 2013;28:755-762.*

2. Predictors of dementia in Parkinson's disease; findings from a 5-year prospective study using the SCOPA-COG. Zhu K, van Hilten JJ, Marinus J. *Parkinsonism and Related Disorders 2014;20:980-985.*

3. Course and risk factors for excessive daytime sleepiness in Parkinson's disease. *Parkinsonism and Related Disorders 2016;24:34-40.*

4. The course of insomnia in Parkinson's disease. Zhu K, van Hilten JJ, Marinus J. *Parkinsonism and Related Disorders 2016;33:51-57.*

5. Associated and predictive factors of depressive symptoms in patients with Parkinson's disease. Zhu K, van Hilten JJ, Marinus J. *Journal of Neurology 2016;263:1215-1225.*

6. Onset and evolution of anxiety in Parkinson's disease. Zhu K, van Hilten JJ, Marinus J. *European Journal of Neurology 2017;24:404-411.*

# Curriculum Vitae

Kangdi Zhu was born on June 16th, 1990 in Wuhan, China (Hubei province). He moved to the Netherlands in 1999, at the age of nine. In 2002, he started VWO (junior high school) at Theresialyceum in Tilburg, where he graduated cum laude in the profiles (Natuur & Techniek and Natuur & Gezondheid).
In 2008, he started medicine at the University of Leiden, where he soon became interested in Neurology in the first year of his studies. In the second year, he became a student-assistant at the department of anatomy, where he taught neuro-anatomy dissection courses for first-year medical students for the next two years.
It was also during this second year, that he obtained the MD/PhD grant for excellent medical students for combining research during their medical study. He soon joined the research team of PROfiling Parkinson's disease (PROPARK) at the department of neurology at the Leiden University Medical Center, led by Professor Bob van Hilten.
During the first two years, he mainly focused on gaining insight in statistical methods that were required in performing the analysis for his project. He participated in several courses in statistics and clinical epidemiology (survival analysis, repeated measurements and masterclass clinical epidemiology in Noordwijk). In 2014, he started his clinical internships and during this period, he finished his first two publications on predictors for hallucinations and dementia in Parkinson's disease. After graduating in 2014, he obtained a full-time MD/PhD grant to finish his PhD within a period of two years. During this time, he managed to publish another four publications on the subject of predictors in Parkinson's disease (insomnia, excessive daytime sleepiness, depression and anxiety).

Kangdi Zhu is currently working as a medical doctor at the department of neurology in Reinier de Graaf hospital in Delft, where he is gaining more clinical experience in Neurology. He is also working on a review on all the longitudinal studies on the subject of clinical predictors in motor- and non-motor complications in Parkinson's disease, together with Dr. Marinus and Professor van Hilten.

## Acknowledgments

This thesis could not have been established without the help of our patients, who took the time and effort to participate in all the annual assessments.

I'd like to thank Bob and Han for their great support, the great working experience, and for believing in me in all those years. Bob was always full of interesting new ideas and Han was the person answer for any problem regarding the statistical or methodological aspect of those ideas. It was a great team to work with and I couldn't have written this thesis without them. I'd also like to use this chance to also thank dr. Dagmar Verbaan and Jorine van der Heeden, who put great time and effort to give life and form to the PROPARK dataset as it is at the moment. Dr. Hein Putter, who gave really helpful insight from a statistical perspective at the beginning of our project.

I'd like to thank my parents, who always stood my side during my medical study and my PhD period.

I'd also like to thank my supervisors in the clinic at Reinier de Graaf in Delft, who showed interest in the progress of my PhD Thesis and gave me the opportunity to work on this thesis whenever this was necessary.

Many thanks to the thesis committee for evaluating my thesis.

I'd like to thank my friend and colleague Laura, for being a great companion at international meetings and for giving me inspiration and insight for new ideas.

Last but not least, I'd like to thank my lovely fiancé Katja, who gave me strength and support.