Clinical Predictors of disease progression in Parkinson's disease

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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]

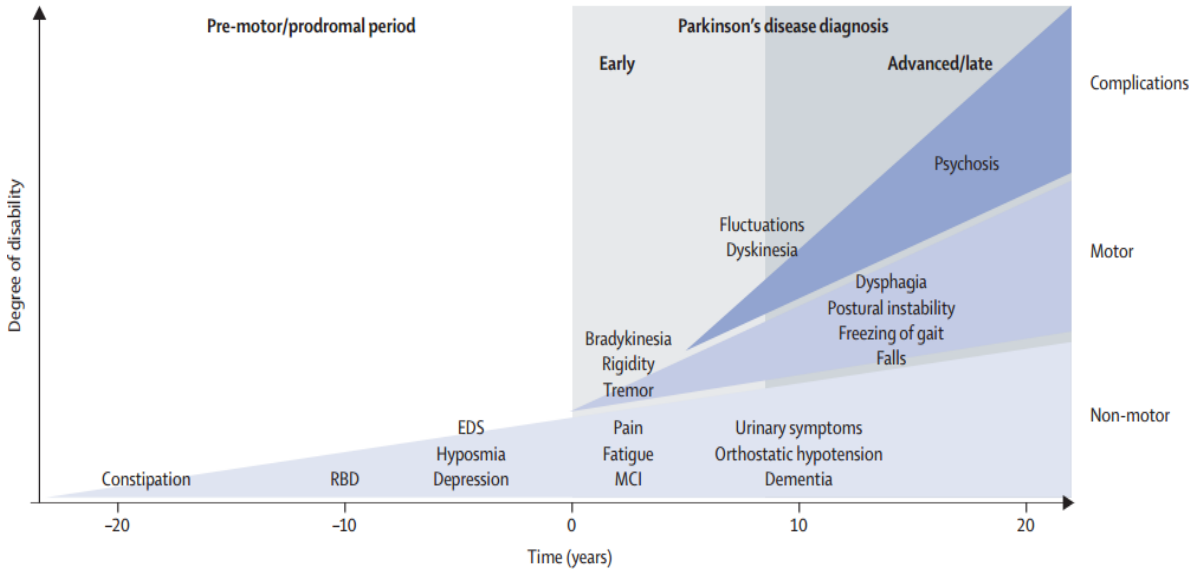
Symptom	Definition
Motor fluctuations	Alterations between periods of good motor symptom control (i.e., on-time) and periods of reduced motor symptom control (i.e., off -time)
Non-motor fluctuations	Alterations between good non-motor symptom control and periods of reduced non-motor symptom control
Dyskinesia	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

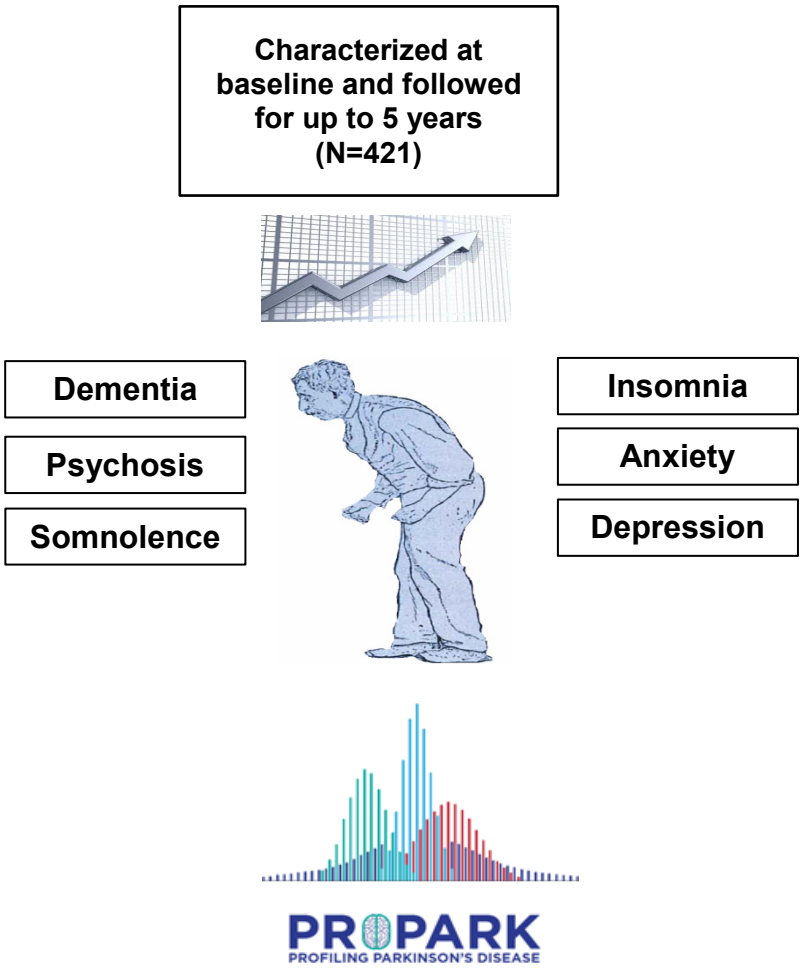
Due to other conditions
- Medical conditions
    - Arthritis
    - Cardiac or pulmonary disorders
    - Reflux
    - Infections
    - Prostate hypertrophy
    - Pain not due to PD
- Medication used to treat medical conditions
- Withdrawal from sedative/hypnotics
- Emotional conditions
    - Stress
 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