Summary
Parkinson's disease (PD) is the second most prevalent neurodegenerative disease after Alzheimer's disease and will be an increasing burden in the near future. The prevalence of PD in industrialized countries is estimated 0.3% in the general population. In a pooled estimate for the European population the prevalence is 1.6% for all people aged older than 65 years. There is an increase with age to 3.5% in the oldest age groups. In this thesis the main aim was to study the clinical profile and the prognosis of (early) PD. Therefore, we formed a large clinical cohort of patients with PD and we followed the patients for three years. Potential prognostic factors (clinical features, comorbidity, and cognitive impairment) and several outcome measures (motor impairment, disability, and quality of life (QoL)) were assessed during follow-up. Because the assessment of impairments and the assessments of physical disability form an essential part of the thesis, two chapters specifically concentrate on clinimetric issues.

The Unified Parkinson's Disease Rating Scale (UPDRS) is widely used for the clinical evaluation of PD. It was unclear whether the UPDRS motor examination (UPDRS-ME) could be reliably applied by non movement disorders specialist (MDS). In chapter 2 therefore, we describe the rater variability of the UPDRS-ME of nurse practitioners, residents in neurology and a MDS compared to a senior MDS. The weighted kappa and ICC statistics indicated good to very good inter-rater and intra-rater reliability for the majority of individual UPDRS-items and the sum score of the UPDRS–ME in all raters. However for inter-rater agreement, it appeared that both nurses, residents, and the MDS consistently assigned higher scores than the senior MDS. The intra-rater 95% repeatability limits were rather wide. We concluded that there was considerable difference for the whole range of UPDRS-ME scores between a senior MDS and nurse practitioners, residents in neurology, and a MDS. This implies that the amount by which raters may disagree should be quantified before starting longitudinal studies of disease progression or clinical trials. Finally, evaluation of rater agreement should always include the assessment of the extent of bias between different raters.

To evaluate symptomatic treatment in early disease, the activities of daily living (ADL) part of the UPDRS is frequently used, however, this part of UPDRS is confounded by items that examine patient's perceptions of primary disease manifestations (e.g., tremor and salivation). Therefore in chapter 3, we present a new generic instrument to measure level of ADL in PD patients: the AMC linear Disability Score (ALDS). The internal consistency reliability of the ALDS was good with 55 items extending the sufficient item-total correlation criterion. The ALDS was correlated with other disability measures and decreasingly associated with measures reflecting impairments and mental health. The ALDS discriminated between more or less severe extra-pyramidal symptoms and patients...
with postural instability showed lower ALDS scores compared to patients without postural instability. Compared to the Schwab and England scale (score 100% = 19%), the ALDS had less ceiling effect (5%). We concluded that the ALDS is a flexible, feasible, and clinimetrically promising instrument to assess the level of disability in newly diagnosed PD patients.

Prior to the cohort study we performed a systematic review of the literature to describe the course of PD and try to identify factors that predict change in motor impairment, disability, and QoL \(\text{(chapter 4)}\). We screened 1535 titles and abstracts, and 27 fulfilled our inclusion criteria. A meta-analysis to quantitatively aggregate progression scores of motor impairment and disability was not possible due to the wide variety of outcome measures used and the heterogeneous study populations. Limited evidence is found for lower UPDRS-ME at baseline, dementia, and SE<70% as prognostic factors for future motor impairment. There is strong evidence for higher age at onset and higher postural instability and gait difficulty-score; and limited evidence for higher bradykinesia-score, non-tremor dominant subtype, symmetrical disease at baseline, and depression as prognostic factors for progression of disability.

Cognitive disturbances are an important part of PD. In \text{chapter 5}, we describe the frequency and pattern of cognitive dysfunction in patients with newly diagnosed PD and identify its demographic and clinical correlates. Relative to controls, PD patients performed significantly worse on most cognitive measures. However, further analysis revealed that group differences in cognitive performance could mainly be explained by immediate memory and executive function. Comparison with normative data showed that impairments were frequent on measures of executive function, memory, and psychomotor speed. Twenty-four percent of PD patients (4% of controls) displayed defective performance on at least three neuropsychological tests and were classified as cognitively impaired. Late onset of disease was an independent predictor of cognitive dysfunction in PD.

PD is a heterogeneous disease. In \text{chapter 6}, we explored the clinical heterogeneity in newly diagnosed PD. We used cluster analysis and described subgroups in terms of impairment, disability, perceived QoL, and use of dopaminergic therapy. Cluster analysis with a two-cluster solution identified a younger and older age group. The three-cluster solution identified an intermediate group with respect to age. In both cluster solutions the older onset group progressed faster and suffered more motor impairments. The intermediate older onset group in the three cluster solution was characterized by more anxiety and depressive symptoms. Increasing age at disease onset was significantly associated with higher Hoehn and Yahr stages, level of disability, and lower perceived QoL.
In chapter 7 and 8, we identified factors that independently contribute to disability and QoL in patients with mild to moderate PD. In the baseline data axial impairment (postural instability and gait difficulty) explained the largest proportion of variance in disability. Bradykinesia and comorbidity contributed to disability, but to a lesser extent. Self-reported mood symptoms and axial impairment were the two factors strongly associated with poorer QoL. Comorbidity and bradykinesia contributed to the explanatory power. Analyses of the three year follow-up data showed that motor impairment progressed with three points per year. Furthermore, a slight progression of disability and QoL was noted. Older age at onset predicted worse motor impairment, more disability, and poorer QoL. Non-dopaminergic reactive symptoms (axial impairment) contributed to more disability and poorer QoL. Comorbidity contributed to disability, but to a lesser extent. Self-reported mood symptoms and comorbidity were associated with poorer QoL. Female sex is associated with a slower progression of motor impairment and QoL.

In chapter 9, the findings of the previous chapters and the implications for clinical practice and future studies are discussed.