Clinimetrics, clinical profile and prognosis in early Parkinson’s disease

Post, B.

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Prognostic factors for the progression of Parkinson’s disease; a systematic review

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Abstract

Objective
The purpose of this systematic review is to summarize studies that describe the course of Parkinson’s disease (PD) and to identify factors that predict change in motor impairment, disability, and quality of life.

Methods
A literature search was conducted in MEDLINE, EMBASE, CINAHL, and Web of Science limited to the English, French, German, Spanish and Dutch language. Reports were selected if the study involved subjects with PD, the outcome measures described impairment, disability or quality of life and follow-up was at least six months. All included studies were scored for methodological quality. Data were extracted and summarized in a best evidence synthesis.

Results
We screened 1535 titles and abstracts, out of which 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 PIGD-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.

Conclusion
Prognostic factors were identified for impairment and disability. The literature on prognosis in PD is not fulfilling the high methodological standards applied nowadays. There is a need for prospective cohorts of PD patients assembled at a common early point in the disease with long time follow-up.
Introduction

Parkinson’s disease (PD) was first described in 1817 by James Parkinson and is one of the oldest known and second most common neurodegenerative disease. The prevalence of PD in industrialised countries is 0.3% in the general population and about 1% in the population older than age 60 years.(1) PD is a progressive disease characterized by bradykinesia, rigidity, tremor, and postural instability.(2) Nowadays more emphasis is put on non-motor features like neuropsychiatric symptoms, sleep disorders, autonomic symptoms, and sensory symptoms.(3) Both motor and non-motor symptoms have a major impact on activities of daily living and quality of life.(4)

Describing functional status and its determinants is important for several reasons; 1) to guide clinical decision making, especially treatment selection and patient counselling; 2) to improve the understanding of the disease process; and 3) to improve the design and analysis of clinical trials (e.g. risk stratification on the basis of important prognostic factors).(5)

Over the last forty years several studies specifically addressed progression of parkinsonian signs (2,6,7) and functional decline.(8) Furthermore, data of clinical trials gave an impression of disease progression, but these were selected populations of mostly young patients without co-morbidity.(9) Marras conducted the first systematic review to identify predictors of motor decline and disability in patients with PD.(10) Recently practice parameters of the American Academy of Neurology (AAN) were published reviewing the prognostic factors for motor progression, dementia, and mortality.(11) These studies showed that early cognitive impairment and baseline severity of motor symptoms are predictors of future motor impairment and disability. Additionally, older age at onset and lack of rest tremor at onset also predict future disability. However the systematic review conducted by Marras only used the MEDLINE database and selected English and French literature. The AAN only reviewed English literature written after 1990.

The aim of this systematic review is to describe the progression of PD and to identify factors that predict motor impairment, disability and quality of life using best evidence synthesis.(12) For this purpose we performed a literature search in several computerised databases, selected relevant articles on the basis of pre-specified inclusion criteria, assessed their methodological quality, and extracted the data of the progression of PD and it’s prognostic factors.

Methods

We report according to a consensus statement for the meta-analysis of observational studies in epidemiology.(13)
Data source and search

A literature search was conducted in the following databases: Medline (1966-November 2004), Embase (1980-November 2004), Cinahl (1982- November 2004), Web of science (1988-November 2004). According to recommendations of Altman (5) and McKibbon (14) the following key words were selected: Parkinson’s disease, incidence, follow-up studies, prognosis, prediction, course, disability, and quality of life. The searches were limited to human studies and the English, French, German, Spanish and Dutch language.

Study selection

The selection procedure was performed in two stages by two independent reviewers (BP and JDS). At first the selection was based upon the title and the abstract, as obtained by the search, considering the inclusion / exclusion criteria. The inclusion criteria were: 1) the study population consists of people with a diagnosis of PD; 2) one or more outcome measures that evaluate motor impairment (Unified Parkinson’s Disease Rating Scale (UPDRS)), disabilities (Schwab & England activities of daily living scale (SE), Hoehn and Yahr staging scale (HY)) or quality of life; and 3) the study has to address changes in the level of functioning over time, i.e. a period longer than 6 months. Randomized clinical trials, when reporting on efficacy, were excluded. Only full length articles or full written reports were considered for inclusion; whether or not they were published. The results of this abstract selection were discussed; in case of disagreement the final decision on inclusion was based on the full length article. Secondly, the full length articles of all selected abstracts were retrieved and assessed according to the same inclusion and exclusion criteria as described above. In case of disagreement between the two reviewers a third independent reviewer (MM) was consulted who made the decision.

The reference lists of the finally selected articles were searched for relevant articles. Furthermore experts were contacted for relevant articles concerning natural history and prognosis of PD.

Data extraction and methodological quality

Study methods and results were extracted by one of the authors (BP). Data were extracted on study design, setting and study population, mean disease duration at baseline, length of follow-up, loss to follow-up, outcome measures, results and prognostic factors. We described the results of each outcome measure as well as the concerning statistics if reported by the authors. Furthermore we listed all factors analyzed (univariate and multivariate) by the authors as potential prognostic factors of impairment, disability or quality of life.
Two reviewers (BP and MM) independently assessed the methodological quality of all the definitive selected publications, using a predefined standardised set of 14 criteria. The criteria were divided into six categories (study population, study size, follow-up, outcome measures, prognostic factors, and analysis and data presentation) and included items for both internal and external validity. Each criterion was rated as positive, negative or inconclusive. Inconclusive was assigned if a criterion was incompletely specified. When no information was present a negative score was given. We discussed conflicting scores until consensus was reached. A more detailed explanation of the criteria is given in Appendix 1. The criteria for methodological quality were based upon general recommendations for studying prognosis (5,15,16) and methodological quality instruments developed by Borghouts (17) and Kwakkel. (18) The criteria were adapted and modified for the purpose of this review. A total score was obtained by summing up the number of criteria rated as positive (one point; range 0-14). All items were assumed to be of equal importance and were not weighted. A study was arbitrarily rated as high quality if a score of nine or higher was obtained.

Results

Search and study selection

Figure 1 shows the results of the search and study selection. We screened 1535 titles and abstracts, out of which 124 full length articles were selected for further review (complete reference list available on request). Of these 21 articles fulfilled the inclusion criteria. (2,6,8,9,19-35) The other 103 articles were excluded: 25 studies investigated population with parkinsonism and not PD, 32 had a follow-up of less the six months, 35 articles did not report one of the pre-specified outcome measures (mortality 18; dementia/cognitive decline 10; rest 7) and 11 articles were excluded for other reasons (trial 2; review 2; rest 7). Checking the reference list and consulting experts resulted in another six articles which fulfilled our inclusion criteria. (7,36-40) Altogether 27 articles were obtained that described the progression of PD and identified prognostic factors for the outcome measures impairment, disability and quality of life. (2,6-9,19-40)

Study characteristics

Table 1 (page 82) summarizes the methodological characteristics of all included studies. All studies were cohort studies of which nine studies were prospective (7,9,19,20;30-32,34,36), eight studies retrospective (2,6,21,23,28,29,38,40) and the other 10 a combination of prospective and retrospective. (8,22,24-27,33,35,37,39) Almost all studies were hospital based, only two studies recruited patients from the general population (7,32)
Figure 1. Search and study selection.


1535 titles and abstracts

The selection procedure was performed by two independent reviewers. At first the selection was based upon the title and the abstract, as obtained by the search, considering pre-specified inclusion / exclusion criteria. Selection of 124 full length articles

21 articles included

Exclusion reasons (prespecified)

Study population not PD 25
Follow-up < 6 months 32
Outcome measure not prespecified 35
   Mortality 18
   Dementia/Cognitive decline 10
   Rest 7
Other 11
   Trial 2
   Review 2
   How to measure mortality 1
   Measuring placebo effect 1
   Not full length article 2
   Outcome not well described 3

TOTAL 103

6 extra added after screening references and consulting experts

Total selection of 27 articles describing 34 outcome measures (one article can describe more then one outcome measure)

Outcome measures:

Impairment 8 (6 times in high quality article) (8 articles)
Disability 24 (8 times in high quality article) (22 articles)
Quality of life 2 (2 times in high quality article) (2 articles)

and one recruited patients in a nursing home. The mean follow-up ranged from 12 to 144 months. In several studies there was a wide variability in follow-up period for each individual patient. The mean disease duration at baseline ranged from 23.5 months (19) to
9.7 years. Out of 27 studies, eight focussed on impairment, 22 on disability, and two on quality of life (more then one outcome measure possible in one study) (Figure 1).

**Methodological quality**

Table 1 (page 82) displays the methodological quality. The overall interrater agreement of the methodological quality assessment was good (overall agreement 81%; ICC 0.77). There was disagreement on 69 items all of which were resolved after discussion. Mean methodological quality was 7.9 (SD 2.8) with a range of 2 to 13. Eleven out of 27 (41%) were considered to be high quality articles when applying the cut-off score of 9 or higher. Of these 11 high studies six described impairment, eight disability and two quality of life (more then one outcome measure possible in each study).

**Reporting outcome measures and prognostic factors**

Due to heterogeneity on study characteristics and methodological quality only a qualitative synthesis (best-evidence synthesis) (12) of the available evidence was possible. Hence only the high quality studies were described in depth for each outcome measure. Regarding prognostic factors we described the levels of evidence for each prognostic factor using an ordinal scale previously used in another systematic review. (41) The levels of evidence ranged from strong evidence to no evidence (Appendix 2).

**Motor impairment: course and prognostic factors**

Detailed information on the eight articles that focused on motor impairment is given in Table 2A (page 88). Six articles were classified as high quality studies. Three of these (6,7,35) reported on the course of motor impairment using the UPDRS-ME. The prognostic factors of motor impairment were described in four high quality studies (6,7,19,30); two studies used the modified Columbia score and the other two used the UPDRS-ME as outcome measure.

Louis reported an annual rate of increase of the UPDRS-ME of 1.5%. (7) When looking at subscores (tremor/bradykinesia/rigidity/gait and balance) of the UPDRS-ME only the tremor score showed no significant progression during the follow-up period. Ruiz (35) described a cohort of newly diagnosed patients with a mean baseline UPDRS-ME score (without treatment) of 17.7. After five years of treatment the UPDRS-ME score was for the first time higher (score 18.8) then the untreated baseline score. The third study (6) described two groups of PD patients one with HY II and one with HY III. A significant change in the total UPDRS-ME score from 38.1 to 41.7 in the HY III group was reported. Both groups in this study revealed a significant decline in the bradykinesia sub-score as opposed to tremor and rigidity sub-scores.
Regarding prognostic factors conflicting results were reported. The Sydney multi-centre study identified age at onset and older age at entry into the study as the significant prognostic factors in multivariate analysis.\(^{(19,30)}\) Louis \(^{(7)}\) could not confirm both prognostic factors for progression of motor impairment but identified the following baseline factors predictive of higher UPDRS-ME score at each annual visit; dementia, SE <70\% and long disease duration (>6.8 years). Goetz \(^{(6)}\) showed that baseline disease duration did not affect the rate of progression of motor impairment. Furthermore, this study described a higher rate of progression in patients with lower initial UPDRS-ME scores.

**Disability: course and prognostic factors**

The majority of the 27 selected articles (n=22) focused on disability (Table 2B, page 90). In total seven articles (32\%) were rated as high quality studies, which described eight outcome measures concerning disability. The course of progression of disability was described in four of these articles \(^{(8,19,35,36)}\) and all but one described prognostic factors for progression of disability in PD.\(^{(8,28,30,31,35,36)}\) Starkstein \(^{(36)}\) described progression on the HY staging scale from 3.2 at baseline to 3.9 after one year in the major depression group. In this study the Northwestern disability scale showed an increase from 16.0 to 18.7 in the major depression group during a twelve month follow-up period. The Sydney multi-centre study group \(^{(19)}\) studied a cohort of 126 patients of which 83 at baseline were HY stage I or II and 43 HY stage III, the median time of progression in the HY I or II group was 3.5 years to HY stage III, seven years to HY stage IV and six years to HY stage V. In the group with HY III at baseline the median time of progression of was 4.5 years to HY IV and 6.5 years to HY V. The group with HY stage I or II had a mortality-rate at 10 years of follow-up of 34.9\%, in the group with HY stage III this was 48.8\%. Jankovic \(^{(8)}\) showed an annual rate of decline in the total UPDRS sum score of 1.3 point in the ON-state and 1.6 in the OFF-state. Similar to motor impairment Ruiz \(^{(35)}\) reported that the UPDRS-ADL and total UPDRS sum score after five years is for the first time worse then at the untreated baseline score.

Regarding prognostic factors Starkstein \(^{(36)}\) showed that major depression, as opposed to minor or no depression, is associated with greater progression on the HY staging scale and the Northwestern disability scale. In the cohort of early PD patients of the Sydney multi-centre study a higher age at onset and symmetrical disease at onset were predictors for faster progression to the onset of balance disorders.\(^{(30)}\) In the DATATOP cohort \(^{(31)}\) a higher postural instability/gait difficulty (=PIGD)-score, a higher bradykinesia score and female sex appeared to be associated with shorter time to disability necessitating L-dopa therapy. Especially for patients with less than 2 years disease duration a high PIGD-
score was particularly troublesome. Non-tremor dominant subtype at onset appeared a prognostic factor for more rapid progression to HY III in another study. (28) Jankovic (8) showed that men, patients with PIGD-subtype (as opposed to tremor subtype) and older age at onset (>57 years as opposed to <57 years) had a more rapid progression of PD as expressed with the UPDRS sum score.

Quality of life; course and prognostic factors

Only two articles reported on quality of life (Table 2C, page 94). Both (32,34) were classified as high quality studies, although the Notthingham health profile is not a validated measure for measuring quality of life in PD. One study (32) observed a decline in quality of life during four years of follow-up when measured with the Notthingham Health Profile (higher score is lower quality of life; proportion with more than 30% increase in score = 58.6%). The other study (34) reported no significant change in quality of life between 0-4 years of follow-up in a cohort with early PD as measured with EuroQol. No prognostic factors were identified in both studies.

Levels of evidence of the identified prognostic factors

Due to heterogeneity in study characteristics and methodological quality a qualitative synthesis of the prognostic factors was performed (Table 3). Limited evidence consists for dementia, SE <70% and lower initial UPDRS-ME scores as prognostic factor for a higher rate of progression of impairment. Furthermore, there is conflicting evidence on age at entry into the study, age at onset and longer disease duration at baseline as prognostic

<table>
<thead>
<tr>
<th>Prognostic factors</th>
<th>Motor impairment</th>
<th>Disability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Higher age at onset</td>
<td>Conflicting evidence</td>
<td>Strong evidence</td>
</tr>
<tr>
<td>Older age at baseline</td>
<td>Conflicting evidence</td>
<td></td>
</tr>
<tr>
<td>Non-tremor dominant subtype at onset</td>
<td></td>
<td>Limited evidence</td>
</tr>
<tr>
<td>Lower UPDRS-ME scores at baseline</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Longer disease duration at baseline</td>
<td>Conflicting evidence</td>
<td>Limited evidence</td>
</tr>
<tr>
<td>Dementia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SE &lt; 70%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PIGD-score</td>
<td>Strong evidence</td>
<td></td>
</tr>
<tr>
<td>Bradykinesia-score</td>
<td>Limited evidence</td>
<td></td>
</tr>
<tr>
<td>Symmetrical disease at baseline</td>
<td>Limited evidence</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depression</td>
<td>Conflicting evidence</td>
<td></td>
</tr>
</tbody>
</table>

UPDRS-ME = Unified Parkinson’s Disease Rating Scale - motor examination; SE = Schwab and England disability scale; PIGD-score = postural instability/gait difficulty–score; empty cells mean there is no evidence available. The outcome measure quality of life was left out because no prognostic factor good be identified.
factors for progression of motor impairment. Strong evidence was found for higher age at onset and higher PIGD-score at baseline as prognostic factors for more rapid progression of disability in PD. Limited evidence consists for higher baseline bradykinesia-score, non-tremor dominant subtype at onset, symmetrical disease onset and depression as prognostic factor of more rapid progression of disability. There is still conflicting evidence on whether sex is a prognostic factor for the progression of disability in PD. No evidence is reported on prognostic factors for the progression of quality of life in PD.

Discussion

The selected articles showed progression of impairment and disability and conflicting evidence on the change of quality of life in PD. A formal meta-analysis to quantitatively aggregate progression scores of motor impairment, disability, and quality of life was not possible due to the wide variety in outcome measures used and heterogeneous study populations. Accordingly only a qualitative synthesis of the prognostic factors was possible. Our review showed limited and conflicting evidence with regard to prognostic factors for motor impairment deterioration. Strong evidence was found for higher age at onset and higher PIGD-score at baseline as prognostic factors for more rapid progression of disability in PD. No evidence was found for prognostic factors on quality of life.

Comparing our results to two previous published reviews (10,11) there are some problems in interpretation. In the practice guidelines of the AAN (11), the outcome measure is motor progression containing both outcome measures describing impairment (UPDRS-ME) and disability (HY or time to HY III). We studied these outcome measures separately. As opposed to the AAN practice guidelines we did not find any evidence in high quality studies that co-morbidities may be used to predict motor progression. Furthermore we found conflicting evidence on sex as a prognostic factor for progression of disability in PD, whereas the AAN states that male sex predicts a faster rate of motor progression. The results of the systematic review written by Marras (10) are more in line with our results. We also found cognitive impairment as prognostic factors for the progression of motor impairment. Furthermore we found a lower UPDRS-ME score at baseline as a prognostic factor for more rapid motor impairment, whereas Marras described the opposite. Our review identified more problems in daily live (SE<70%) as a prognostic factor for progression in motor impairment which were not described by Marras. Like Marras we found higher age at onset and lacking rest tremor as important factors in predicting disability. We found no evidence in our high quality studies on higher UPDRS-ME score at baseline and cognitive impairment as prognostic factors for the progression of disability as opposed to Marras. Our review added higher PIGD-score, higher bradykinesia-score,
symmetrical disease at baseline, and depression as prognostic factors for the progression of disability in PD. Although it can be defended that higher UPDRS-ME scores as found by Marras strongly correlate with higher bradykinesia and higher PIGD score and so these are no new prognostic factors.

To examine the validity of our search we compared our final selection to the two previous published systematic reviews. Marras included thirteen studies (2,6-8,19,25,26,30,36-40) in her review of which we identified 11 in our search (2,6-8,19,25,26,30,36,39,40). The other two articles were added to our review (37,38). When applying our criteria for methodological quality to the articles included in the review of Marras six articles (6-8,19,30,36) were rated as high quality articles. When comparing our selection of articles with the seven articles included in the practice guideline of the AAN, only two articles of these were included in our review (8,28) and five were not (42-46). Two of these latter five (42,44) were initially missed by our search. Both articles were retrieved and eventually excluded from our review because they did not describe one of the pre-specified outcome measures. The other three of these five articles (43,45,46) were identified by our search but excluded because they did not meet an inclusion criteria used; two of them had a follow-up of less then six months (43,45) and one (46) used the outcome measure mortality and medical service utilisation. Strikingly, only one article (8) was included in both the review of Marras and the AAN. Marras (10) only searched the MEDLINE database; the AAN (11) excluded articles published before 1990 and only searched the English literature. We searched several databases without restriction to publication date and with less stringent language criteria. Therefore we are convinced that our search did not miss essential articles regarding our pre-specified outcome measures. Furthermore it adds information to the other two reviews because it is the most extensive and thoroughly executed.

The methodological quality according to our criteria list was rather low. Overall only 11 out of 27 included articles (41%) were of high quality according to our pre-defined cut-off score (6-8,19,28,30-32,34-36). The most prevalent methodological shortcomings appeared to be selection of study population, information completers versus drop-outs/loss to follow-up, description of inclusion/exclusion criteria and analysis techniques. Especially the poor results regarding selection of study population are striking because identifying patients at an early common point in the course of the disease is important for the assessment of prognosis. One of the explanations may be that 11 out 27 (41%) articles were published before 1990 (2,20-23,25-27,37,3840) and are not fulfilling the high standards of methodological criteria used nowadays. Furthermore around 1990 the case definition of PD changed (47,48) and the use of the UPDRS (49) as standard outcome measure was implemented. These developments seem to be a turning point in the methodology of PD research. Post-hoc analysis of the methodological quality
dichotomizing the studies in before and after 1990, showed a mean quality score of 5.8 (0.6) with a range of 5 to 7 before 1990 (2,20-23,25-27,37,38,40) and a mean quality of 9.3 (2.9) with a range of 2-13 after 1990 (6-9,19,24,25,28-36,39), a statistically significant difference (Mann-Whitney U test p = 0.002). All high quality articles retrieved in the present review were published after 1990 (Table 1, page 82). The outcome measurement was compromised by the variety and drawbacks of applied outcome measures in the individual studies. This problem is addressed for future studies with the development of the new-UPDRS and by adding an appendix of recommended scales for measuring several aspects of outcome in PD.(50,51)

Our results show that the literature on prognosis in PD is not fulfilling the high quality standards on methodology applied nowadays. There is a need for prospectively followed cohorts of PD patients assembled at a common early point in the disease with extended follow-up time. Special attention should be given to the ongoing assessment of the diagnosis of PD and finally the long term aim of securing pathological data through post mortem analysis for definitive diagnosis. Analysis of prognostic factors should include multivariate analysis to account for confounding factors.(5) There is a need for further exploring the prognostic factors for progression of PD to guide clinical decision making, especially treatment selection and patient counselling, to improve the understanding of the disease process, and to improve the design and analysis of future (neuro-protective) clinical trials.(5)

Conclusion

This report summarizes the course and prognostic factors for the progression of PD. Limited evidence is found for lower UPDRS-ME at baseline, dementia and SE<70% as prognostic factors of future motor impairment. Furthermore there is strong evidence for higher age at onset and higher PIGD-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. No evidence is found for predictors for future quality of life in PD. These results will help us in the care for our patients, improve the design and analysis of trials, and improve our understanding of the disease process.
<table>
<thead>
<tr>
<th>Study (reference)</th>
<th>Methodological quality score</th>
<th>Setting</th>
<th>Design</th>
<th>Number participants</th>
<th>Diagnostic criteria for PD</th>
<th>Disease duration at baseline (mean (SD))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Starkstein, 1992 (36)</td>
<td>10</td>
<td>Hospital PC 105</td>
<td></td>
<td></td>
<td></td>
<td>9.7 (6.4) years</td>
</tr>
<tr>
<td>Hely, 1995 (30)</td>
<td>13</td>
<td>Hospital PC 136</td>
<td>Described in article; the presence of two of the following (tremor / bradykinesia / rigidity) in the absence of features suggestive of atypical parkinsonism.</td>
<td></td>
<td>23.5 (20.4) months</td>
<td></td>
</tr>
<tr>
<td>McDermott, 1995 (31)</td>
<td>12</td>
<td>Hospital PC 800</td>
<td></td>
<td></td>
<td></td>
<td>2.1 years</td>
</tr>
<tr>
<td>Roos, 1996 (28)</td>
<td>10</td>
<td>Hospital RC 345</td>
<td>UK Parkinson’s disease Society Brain Bank</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Louis, 1999 (7)</td>
<td>10</td>
<td>Population PC 237</td>
<td>UK Parkinson’s disease Society Brain Bank</td>
<td></td>
<td>6.8 (6.8) years</td>
<td></td>
</tr>
<tr>
<td>Hely, 1999 (19)</td>
<td>11</td>
<td>Hospital PC 136</td>
<td>Described in article; the presence of two of the following (tremor / bradykinesia / rigidity) in the absence of features suggestive of atypical parkinsonism.</td>
<td></td>
<td>23.5 (20.4) months</td>
<td></td>
</tr>
<tr>
<td>Karlsen, 2000 (32)</td>
<td>12</td>
<td>Population PC 245</td>
<td>Own PD criteria; at least 2 out 4; tremor / rigidity / bradikinesia / postural abnormalities; and no atypical signs; and no other etiology for Parkinsonism</td>
<td></td>
<td>8.5 years</td>
<td></td>
</tr>
<tr>
<td>Goetz, 2000 (6)</td>
<td>12</td>
<td>Hospital RC 100</td>
<td>Defined by CAPIT</td>
<td></td>
<td>8.8 years</td>
<td></td>
</tr>
<tr>
<td>Jankovic, 2001 (8)</td>
<td>9</td>
<td>Hospital RC/PC 297</td>
<td>Typical PD; no atypical features during follow-up. Not exactly described, no reference to one of the criteria sets used to date.</td>
<td></td>
<td>6.5 years</td>
<td></td>
</tr>
<tr>
<td>Marras, 2004 (34)</td>
<td>11</td>
<td>Hospital PC 301</td>
<td>UK Parkinson’s disease Society Brain Bank</td>
<td></td>
<td>1.7 years</td>
<td></td>
</tr>
</tbody>
</table>

Grey cells mean high quality study.
### Table 1. Methodological characteristics of observational studies on the progression of PD and it's prognostic factors.

<table>
<thead>
<tr>
<th>Study (reference)</th>
<th>Methodological quality score</th>
<th>Setting</th>
<th>Design</th>
<th>Number participants</th>
<th>Diagnostic criteria for PD</th>
<th>Disease duration at baseline (mean (SD))</th>
<th>Follow-up (years or months)</th>
<th>Loss to Follow-up</th>
<th>Outcome measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Starkstein, 1992 (36)</td>
<td>10</td>
<td>Hospital PC</td>
<td>105</td>
<td>9.7 (6.4) years</td>
<td>12 months</td>
<td>Rating scale for symptoms of PD (own developed instrument; impairment); HY (disability); NDS(disability)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hely, 1995 (30)</td>
<td>13</td>
<td>Hospital PC</td>
<td>136</td>
<td>23.5 (20.4) months</td>
<td>60 months</td>
<td>The onset of disability necessitating L-dopa therapy (disability)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>McDermott, 1995 (31)</td>
<td>12</td>
<td>Hospital PC</td>
<td>800</td>
<td>2.1 years</td>
<td>Mean 12 months</td>
<td>The onset of disability necessitating L-dopa therapy (disability)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Roos, 1996 (28)</td>
<td>10</td>
<td>Hospital RC</td>
<td>345</td>
<td>0/345</td>
<td>UK Parkinson’s disease Society Brain Bank</td>
<td>Time to reach HY III (disability)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Louis, 1999 (7)</td>
<td>10</td>
<td>Population PC</td>
<td>237</td>
<td>6.8 (6.8) years</td>
<td>Mean 3.3 years; all follow-up &gt;1year</td>
<td>UPDRS-ME (impairment)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hely, 1999 (19)</td>
<td>11</td>
<td>Hospital PC</td>
<td>136</td>
<td>23.5 (20.4) months</td>
<td>120 months</td>
<td>Time to reach HY III (disability)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Karlsen, 2000 (32)</td>
<td>12</td>
<td>Population PC</td>
<td>245</td>
<td>8.5 years</td>
<td>48 months</td>
<td>UPDRS-ME (impairment)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Goetz, 2000 (6)</td>
<td>12</td>
<td>Hospital RC</td>
<td>100</td>
<td>Defined by CAPIT</td>
<td>8.8 years</td>
<td>Patients derived from computer base inventory to identify all new patients with PD between 1992 and 1998 who were already on levodopa and whose HY at first presentation was HY II or III; within this group patients with a stable PD diagnosis within 4 years were identified (221); from this cohort two groups were made for analysis HY II 50; HY III 50</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jankovic, 2001 (8)</td>
<td>9</td>
<td>Hospital RC/PC</td>
<td>297</td>
<td>Typical PD; no atypical features</td>
<td>6.5 years</td>
<td>Consecutive patients diagnosed with PD in a hospital specialised in PD; followed for at least 3 years, only patients where the PD diagnosis was maintained during the follow-up were included in the study</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Marras, 2004 (34)</td>
<td>11</td>
<td>Hospital PC</td>
<td>301</td>
<td>1.7 years</td>
<td>48 months</td>
<td>Patients derived from computer base inventory to identify all new patients with PD between 1992 and 1998 who were already on levodopa and whose HY at first presentation was HY II or III; within this group patients with a stable PD diagnosis within 4 years were identified (221); from this cohort two groups were made for analysis HY II 50; HY III 50</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean 6.4 years; All follow-up &gt; 3 years</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Consecutive patients diagnosed with PD in a hospital specialised in PD; followed for at least 3 years, only patients where the PD diagnosis was maintained during the follow-up were included in the study</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>48 months</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>111/301</td>
<td>EQ-5D and VAS from Euro-Qol (quality of life)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Table 1. (Continued)

| Study (reference) | Methodological quality score | Study;  
| Setting  
| Design  
<table>
<thead>
<tr>
<th>Number participants</th>
<th>Diagnostic criteria for PD</th>
<th>Disease duration at baseline (mean (SD))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ruiz, 2004 (35)</td>
<td>9</td>
<td>Hospital RC/PC 82</td>
</tr>
<tr>
<td>Hoehn and Yahr, 1967 (2)</td>
<td>6</td>
<td>Hospital RC 271</td>
</tr>
<tr>
<td>Guillard, 1978 (38)</td>
<td>6</td>
<td>Hospital RC 164</td>
</tr>
<tr>
<td>Rinne, 1980 (23)</td>
<td>5</td>
<td>Hospital RC 349</td>
</tr>
<tr>
<td>Maier Hoehn, 1983 (22)</td>
<td>6</td>
<td>Hospital RC/PC 182</td>
</tr>
<tr>
<td>Aimard, 1984 (21)</td>
<td>5</td>
<td>Hospital RC 302</td>
</tr>
<tr>
<td>Curtis, 1984 (20)</td>
<td>7</td>
<td>Hospital PC 176</td>
</tr>
<tr>
<td>Guillard, 1986 (37)</td>
<td>6</td>
<td>Hospital RC/PC 356</td>
</tr>
<tr>
<td>Markham, 1986 (27)</td>
<td>6</td>
<td>Hospital RC/PC 19</td>
</tr>
</tbody>
</table>

Grey cells mean high quality study.
<table>
<thead>
<tr>
<th>Follow-up (years or months)</th>
<th>Loss to Follow-up</th>
<th>Outcome measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>60 months</td>
<td>Initial cohort of 82 patients; during follow-up 23 atypical features; 59 analysed for progression in time</td>
<td>UPDRS-ADL / ME; UPDRS- total score (impairment and disability)</td>
</tr>
<tr>
<td>0-180 months</td>
<td>11/271</td>
<td>HY (disability)</td>
</tr>
<tr>
<td>48-96 months</td>
<td>Time to motor progression (impairment) and time to deterioration in function (disability)</td>
<td></td>
</tr>
<tr>
<td>0-108 months</td>
<td>Own developed disability score (disability)</td>
<td></td>
</tr>
<tr>
<td>0-160 months</td>
<td>HY (disability)</td>
<td></td>
</tr>
<tr>
<td>Median follow-up 2.79 years; 6 months to 17 years</td>
<td>HY (disability)</td>
<td></td>
</tr>
<tr>
<td>144 months</td>
<td>28/176</td>
<td>HY (disability)</td>
</tr>
<tr>
<td>120 months</td>
<td>Time to loss independence (disability)</td>
<td></td>
</tr>
<tr>
<td>144 months</td>
<td>UCLA-scale (disability); HY (disability)</td>
<td></td>
</tr>
</tbody>
</table>
### Table 1. (Continued)

<table>
<thead>
<tr>
<th>Study (reference)</th>
<th>Methodological quality score</th>
<th>Study; Setting, Design, Number participants</th>
<th>Diagnostic criteria for PD</th>
<th>Disease duration at baseline (mean (SD))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Goetz, 1988 (40)</td>
<td>6</td>
<td>Hospital RC 31</td>
<td>Own criteria described in article; the presence of two of the following (tremor/bradykinesia/rigidit; /but not impaired postural and righting reflexes) in the absence of features suggestive of atypical parkinsonism.</td>
<td>13.3 months</td>
</tr>
<tr>
<td>Diamond, 1989 (26)</td>
<td>6</td>
<td>Hospital RC/PC 54</td>
<td>Not described other than idiopathic PD and exclusion of post-encephalitic parkinsonism.</td>
<td></td>
</tr>
<tr>
<td>Diamond, 1990 (25)</td>
<td>5</td>
<td>Hospital RC/PC 70</td>
<td>Not described other than idiopathic PD and exclusion of post-encephalitic parkinsonism.</td>
<td></td>
</tr>
<tr>
<td>Chia, 1992 (24)</td>
<td>8</td>
<td>Hospital RC/PC 215</td>
<td>Own criteria; the presence of two or more of the four cardinal symptoms (tremor, rigidity, bradykinesia and gait disturbance/flexed posture); without an other cause of parkinsonism.</td>
<td>3.4 years</td>
</tr>
<tr>
<td>Di Rocco, 1996 (29)</td>
<td>5</td>
<td>Hospital RC 330</td>
<td>Own criteria; the presence of one or more of the four cardinal symptoms (tremor, rigidity, bradykinesia and impaired balance); without an other cause of parkinsonism.</td>
<td></td>
</tr>
<tr>
<td>Ferraz, 1996 (39)</td>
<td>6</td>
<td>Hospital RC/PC 133</td>
<td>Own criteria; the presence of two or more of the four cardinal symptoms (tremor, rigidity, bradykinesia and postural instability) with good reaction to L-dopa and without atypical features</td>
<td></td>
</tr>
<tr>
<td>Mitchell, 1996 (9)</td>
<td>2</td>
<td>Nursing home residents PC 340</td>
<td>ICD-9-CM</td>
<td></td>
</tr>
<tr>
<td>Gasparoli, 2002 (33)</td>
<td>8</td>
<td>Hospital RC/PC 103</td>
<td>UK Parkinson’s disease Society Brain Bank</td>
<td>Newly diagnosed PD</td>
</tr>
</tbody>
</table>

PD = Parkinson’s disease; HY = Hoehn and Yahr staging scale; MCS = Modified Columbia Score; UPDRS = Unified Parkinson’s Disease Rating Scale; UPDRS-ME = Unified Parkinson’s Disease Rating Scale-motor examination; UPDRS-ADL = Unified Parkinson’s Disease Rating Scale-Activities of Daily Living; PC = Prospective cohort; RC = Retrospective cohort; CAPIT = Core Assessment Program for intracerebral transplantation; UCLA-scale = University of California Los Angeles disability-scale; NDS= Northwestern Disability scale; NHP= Notthingham health profile; ICD-9-CM = International Classification of Diseases-9-Clinical Modification; empty cell means data was not available in the manuscript.
<table>
<thead>
<tr>
<th>Follow-up (years or months)</th>
<th>Loss to Follow-up</th>
<th>Outcome measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean 24.3 months</td>
<td></td>
<td>Progression to HYIII (disability)</td>
</tr>
<tr>
<td>72 months</td>
<td>1/54</td>
<td>UCLA-scale (disability)</td>
</tr>
<tr>
<td>All followed for a minimum of 2 years; 53 followed for 6 years; 6 between 2-6 years follow-up, 9 died.</td>
<td>2/70</td>
<td>UCLA-scale (disability)</td>
</tr>
<tr>
<td>24-180; mean 62.4 months</td>
<td>0/215</td>
<td>HY (disability)</td>
</tr>
<tr>
<td>0/330</td>
<td>Time in months to progress to a successive stage of the Hoehn and-Yahr scale (disability)</td>
<td></td>
</tr>
<tr>
<td>20 months</td>
<td>15/133</td>
<td>HY (disability)</td>
</tr>
<tr>
<td>18 months</td>
<td>0/340</td>
<td>ADL score (own developed instrument; disability)</td>
</tr>
<tr>
<td>60 months</td>
<td>0/103</td>
<td>UPDRS-ME (impairment)</td>
</tr>
</tbody>
</table>

PD = Parkinson’s disease; HY = Hoehn and Yahr staging scale; MCS = Modified Columbia Score; UPDRS = Unified Parkinson’s Disease Rating Scale; UPDRS-ME = Unified Parkinson’s Disease Rating Scale-motor examination; UPDRS-ADL = Unified Parkinson’s Disease Rating Scale-Activities of Daily Living; PC = Prospective cohort; RC = Retrospective cohort; CAPIT = Core Assessment Program for intracerebral transplantation; UCLA-scale = University of California Los Angeles disability-scale; NDS= Northwestern Disability scale; NHP= Nottingham health profile; ICD-9-CM = International Classification of Diseases-9-Clinical Modification; empty cell means data was not available in the manuscript.
Table 2A. Results of observational studies on the course of impairment and its prognostic factors in patients with Parkinson’s disease.

<table>
<thead>
<tr>
<th>Study</th>
<th>Outcome measure</th>
<th>Results</th>
<th>Prognostic factors</th>
<th>Univariate analysis</th>
<th>Multivariate analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Starkstein, 1992 (36)</td>
<td>Own developed rating scale for</td>
<td>No differences in progression rate between the groups major depression, minor depression and no depression</td>
<td>Major depression, minor depression and no depression</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>motor symptoms of PD</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hely, 1995 (30)</td>
<td>MCS increase of &gt;10 points in 5</td>
<td></td>
<td>Dementia and age at onset per 10 years</td>
<td></td>
<td>2.9 (1.4-6.3)</td>
</tr>
<tr>
<td></td>
<td>years</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hely, 1999 (19)</td>
<td>Modified Columbia Score increase</td>
<td></td>
<td>Increasing tremor score, increasing age and female sex.</td>
<td></td>
<td>2.41 (1.24-4.66)</td>
</tr>
<tr>
<td></td>
<td>of &gt;20 points in 10 years</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Louis, 1999 (7)</td>
<td>UPDRS-ME</td>
<td>UPDRS-ME total score: significant annual rate of increase; 1.5 points (1.5%) No difference in disease progression between short disease duration (&lt;3 years) and long disease duration (&gt;3 years). Progression of subscores: Tremor: no significant increase Bradykinesia: significant annual rate of increase; 0.6 points / 28 (2.1%) Rigidity: significant annual rate of increase; 0.4 points / 20 (2.0%) Gait and Balance: significant annual rate of increase; 0.5 points / 16 (3.1%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Goetz, 2000 (6)</td>
<td>UPDRS-ME</td>
<td>UPDRS-ME; in the HY II group no significant change in total UPDRS-ME score 27.8 to 28.3, but in the HY III group there was a significant change in the total UPDRS-ME score 38.1 to 41.7</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ruiz, 2004 (35)</td>
<td>UPDRS-ME</td>
<td>Baseline: UPDRS-ME 17.7 (10) Year 3: UPDRS-ME 14.4 (8.3) Year 5: UPDRS-ME 18.8 (9.6)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Guillard, 1978 (38)</td>
<td>Time to motor progression</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gasparoli, 2002 (33)</td>
<td>UPDRS-ME</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

UPDRS = Unified Parkinson’s Disease Rating Scale; UPDRS-ME = Unified Parkinson’s Disease Rating Scale-motor examination; HY = Hoehn and Yahr staging scale; MCS= Modified Columbia Score; OR = Odds Ratio; empty cell means data was not available in the manuscript; grey cells mean high quality study.
Table 2A. Results of observational studies on the course of impairment and its prognostic factors in patients with Parkinson’s disease.

<table>
<thead>
<tr>
<th>Study</th>
<th>Outcome measure</th>
<th>Results</th>
<th>Prognostic factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Starkstein, 1992</td>
<td>Own developed rating scale for motor symptoms of PD</td>
<td>No differences in progression rate between the groups major depression, minor depression and no depression</td>
<td></td>
</tr>
<tr>
<td>Hely, 1995</td>
<td>MCS increase of &gt;10 points in 5 years</td>
<td>Univariate analysis: Dementia and age at onset per 10 years. Multivariate analysis: Age at onset per 10 years OR 2.9 (1.4-6.3)</td>
<td></td>
</tr>
<tr>
<td>Hely, 1999</td>
<td>Modified Columbia Score increase of &gt;20 points in 10 years</td>
<td>Univariate analysis: Increasing tremor score, increasing age and female sex. Multivariate analysis: Older age OR 2.41 (1.24-4.66)</td>
<td></td>
</tr>
<tr>
<td>Louis, 1999</td>
<td>UPDRS-ME total score: significant annual rate of increase; 1.5 points (1.5%)</td>
<td>No difference in disease progression between short disease duration (&lt;3 years) and long disease duration (&gt;3 years). Progression of subscores: Tremor: no significant increase. Bradykinesia: significant annual rate of increase; 0.6 points / 28 (2.1%). Rigidity: significant annual rate of increase; 0.4 points / 20 (2.0%). Gait and Balance: significant annual rate of increase; 0.5 points / 16 (3.1%). Multivariate analysis: Baseline factors predictive of higher UPDRS-ME total score at each annual visit; dementia (z-score 4.0), SE &lt;70% (z-score 6.8), long disease duration (&gt;6.8 years) (z-score 3.6). No predictors: age at entry into the study, sex, ethnic group, education, age at onset, L-dopa therapy.</td>
<td></td>
</tr>
<tr>
<td>Goetz, 2000</td>
<td>UPDRS-ME; in the HY II group no significant change in total UPDRS-ME score 27.8 to 28.3, but in the HY III group there was a significant change in the total UPDRS-ME score 38.1 to 41.7</td>
<td>UPDRS-ME scores at baseline were negatively correlated with change in UPDRS-ME scores; lower initial scores have higher rate of progression. Baseline disease duration did not affect rate of progression</td>
<td></td>
</tr>
<tr>
<td>Ruiz, 2004</td>
<td>UPDRS-ME Baseline: 17.7 (10) Year 3: 14.4 (8.3) Year 5: 18.8 (9.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Guillard, 1978</td>
<td>Time to motor progression</td>
<td>Slower progression in those with less bradykinesia at onset of L-dopa therapy and in those who are independent at onset of L-dopa therapy</td>
<td></td>
</tr>
<tr>
<td>Gasparoli, 2002</td>
<td>UPDRS-ME Patients with slow evolution were characterized by earlier age at onset, lateralization of parkinsonian signs, prevalence of rest tremor and absence of gait disturbance. Rapid progression characterized by older age, absence of lateralization of parkinsonian signs, predominance of bradykinesia-rigidity and gait-disturbance</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 2B. Results of observational studies on the course of disability and its prognostic factors in patients with Parkinson’s disease.

<table>
<thead>
<tr>
<th>Study</th>
<th>Outcome measure</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Starkstein, 1992 (36)</td>
<td>HY</td>
<td>Major depression: Baseline 3.2; One year 3.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Minor depression; Baseline 3.1; One year 3.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No depression; Baseline 2.6; One year 2.8</td>
</tr>
<tr>
<td></td>
<td>NDS</td>
<td>Major depression; Baseline 16.0; One year 18.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Minor depression; Baseline 13.9; One year 13.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No depression; Baseline 9.9; One year 9.8</td>
</tr>
<tr>
<td>Hely, 1995 (30)</td>
<td>The onset of balance disorders</td>
<td></td>
</tr>
<tr>
<td>Roos, 1996 (28)</td>
<td>Time to reach HY III</td>
<td></td>
</tr>
<tr>
<td>Hely, 1999 (19)</td>
<td>HY</td>
<td>At baseline 83/126 were HY I or II; median time of progression to HY III 3.5 years, to HY IV 7 years and to HY V 6 years; 34.9% died</td>
</tr>
<tr>
<td></td>
<td></td>
<td>At baseline 43/126 were HY III; median time to HY IV was 4.5 years and to HY V 6.5 years; 48.8% died</td>
</tr>
<tr>
<td>Jankovic, 2001 (8)</td>
<td>UPDRS-total score</td>
<td>Annual rate of decline in the total UPDRS (I, II and III) sum score 1.34 in ON and 1.58 in OFF</td>
</tr>
<tr>
<td></td>
<td>(sum of mentation and behaviour; ADL;ME)</td>
<td></td>
</tr>
<tr>
<td>Ruiz, 2004 (35)</td>
<td>UPDRS-ADL</td>
<td>Baseline: UPDRS-ADL 7.8 (4.7)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Year 3: UPDRS-ADL 6.7 (3.4)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Year 5: UPDRS-ADL 8.4 (3.8)</td>
</tr>
<tr>
<td></td>
<td>UPDRS total score</td>
<td>Baseline: Total UPDRS 27.1 (13)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Year 3: Total UPDRS 22.6 (11)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Year 5: Total UPDRS 29.5 (13.8)</td>
</tr>
<tr>
<td>Hoehn and Yahr, 1967 (2)</td>
<td>HY</td>
<td>Disabled (HY stage IV or V) or dead; 1-5 disease 31/110 (28.1%), 6-10 disease 25/41 (61.0%), 11-15 disease 40/48 (83.3%), &gt;15 disease 17/19 (89.5%). Total patients observed 271-42 (cases first observed before 1949)-11 (lost to follow-up) = 229</td>
</tr>
<tr>
<td>Guillard, 1978 (38)</td>
<td>Time to deterioration in function</td>
<td></td>
</tr>
<tr>
<td>Rinne, 1980 (23)</td>
<td>Own developed disability score</td>
<td>Improvement in total disability (% of baseline) ranging from 47% after 1 year of treatment to -10% after 9 years of treatment</td>
</tr>
</tbody>
</table>

Grey cells mean high quality study.
Table 2B. Results of observational studies on the course of disability and its prognostic factors in patients with Parkinson’s disease.

<table>
<thead>
<tr>
<th>Study</th>
<th>Outcome measure</th>
<th>Results</th>
<th>Prognostic factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Starkstein, 1992 (36)</td>
<td>HY Major depression: Baseline 3.2; One year 3.9</td>
<td>Faster progression in patients with Major depression as compared to minor depression / no depression</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Minor depression: Baseline 3.1; One year 3.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>No depression: Baseline 2.6; One year 2.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NDS Major depression: Baseline 16.0; One year 18.7</td>
<td>Faster progression in patients with Major depression as compared to minor depression / no depression</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minor depression: Baseline 13.9; One year 13.4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No depression: Baseline 9.9; One year 9.8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hely, 1995 (30)</td>
<td>The onset of balance disorders</td>
<td>Univariate analysis: Age at onset per 10 years, symmetrical disease, Columbia score per 5 points and bradykinesia score per 5 points. Multivariate analysis: Age at onset per 10 years OR 2.1 (1.1-3.9) Symmetrical disease OR 4.0 (1.3-12)</td>
<td></td>
</tr>
<tr>
<td>McDermott, 1995 (31)</td>
<td>The onset of disability necessitating L-dopa therapy.</td>
<td>Univariate: Patients with poorer scores on most of the UPDRS-derived variables, the staging according to HY, the ADL scale of Schwab and England and the Pegboard test were at a significantly increased risk of reaching the end-point (Table 1) Multivariate: PIGD-score (sum of falling/freezing/walking difficulty by history and gait and postural stability by examination divided by five): HR overall 1.85 (1.32-2.59); &lt;2 years symptom duration 2.87 (1.78-4.63); ≥2 1.34 (0.88-2.04). Bradykinesia score (finger taps/rapid alternating movement/hand movement/legagility/total bradykinesia score by examination): HR 2.13 (1.54-2.94) Sex=Female: HR 1.36 (1.00-1.84)</td>
<td></td>
</tr>
<tr>
<td>Roos, 1996 (28)</td>
<td>Time to reach HY III</td>
<td>Patients with tremor reach this stage significantly later than patients with hypokinesia/rigidity or tremor/hypokinesia/rigidity</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Patients with tremor reach this stage significantly later than patients with hypokinesia/rigidity or tremor/hypokinesia/rigidity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jankovic, 2001 (8)</td>
<td>UPDRS-total score (sum of mentation and behaviour; ADL; ME)</td>
<td>Annual rate of decline in the total UPDRS (I, II and III) sum score 1.34 in ON and 1.58 in OFF Males, patients with PIGD-subtype (sum of falling/freezing/walking difficulty by history and gait and postural stability by examination divided by five) and older age at onset (&gt;57 years as opposed to &lt;57 years) had a less favourable prognosis. (Showing a steeper slope of progression in the repeated measurement analysis)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Trend that patients with tremor at onset progress less slowly, during the first ten years of disease, then patients with other symptoms at onset</td>
<td></td>
</tr>
<tr>
<td>Ruiz, 2004 (35)</td>
<td>UPDRS-ADL Baseline: UPDRS-ADL 7.8 (4.7) Year 3: UPDRS-ADL 6.7 (3.4) Year 5: UPDRS-ADL 8.4 (3.8)</td>
<td>Slower progression in patients with tremor subtype at start of L-dopa therapy. Faster progression in those with Babinski (diagnosis!!!) and in those with psychiatric side effects in first year of treatment with L-dopa therapy</td>
<td></td>
</tr>
<tr>
<td>Hoehn and Yahr, 1967 (2)</td>
<td>HY Disabled (HY stage IV or V) or dead; 1-5 disease 31/110 (28.1%), 6-10 disease 25/41 (61.0%), 11-15 disease 40/48 (83.3%), &gt;15 disease 17/19 (89.5%). Total patients observed 271-42 (cases first observed before 1949)-11 (lost to follow-up) = 229 Trend that patients with tremor at onset progress less slowly, during the first ten years of disease, then patients with other symptoms at onset</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Guillard, 1978 (38)</td>
<td>Time to deterioration in function</td>
<td>Slower progression in patients with tremor subtype at start of L-dopa therapy. Faster progression in those with Babinski (diagnosis!!!) and in those with psychiatric side effects in first year of treatment with L-dopa therapy</td>
<td></td>
</tr>
<tr>
<td>Rinne, 1980 (23)</td>
<td>Own developed disability score</td>
<td>Improvement in total disability (% of baseline) ranging from 47% after 1 year of treatment to -10% after 9 years of treatment</td>
<td></td>
</tr>
</tbody>
</table>

Prognostic factors

- Faster progression in patients with Major depression as compared to minor depression / no depression
- Faster progression in patients with Major depression as compared to minor depression / no depression

Univariate analysis:
- Age at onset per 10 years, symmetrical disease, Columbia score per 5 points and bradykinesia score per 5 points.

Multivariate analysis:
- Age at onset per 10 years OR 2.1 (1.1-3.9)
- Symmetrical disease OR 4.0 (1.3-12)
- PIGD-score (sum of falling/freezing/walking difficulty by history and gait and postural stability by examination divided by five): HR overall 1.85 (1.32-2.59); <2 years symptom duration 2.87 (1.78-4.63); ≥2 1.34 (0.88-2.04).
- Bradykinesia score (finger taps/rapid alternating movement/hand movement/legagility/total bradykinesia score by examination): HR 2.13 (1.54-2.94)
- Sex=Female: HR 1.36 (1.00-1.84)

Patients with tremor reach this stage significantly later than patients with hypokinesia/rigidity or tremor/hypokinesia/rigidity

Males, patients with PIGD-subtype (sum of falling/freezing/walking difficulty by history and gait and postural stability by examination divided by five) and older age at onset (>57 years as opposed to <57 years) had a less favourable prognosis. (Showing a steeper slope of progression in the repeated measurement analysis)

Age at onset did not correlate with clinical deterioration at the final visit

Trend that patients with tremor at onset progress less slowly, during the first ten years of disease, then patients with other symptoms at onset

Slower progression in patients with tremor subtype at start of L-dopa therapy. Faster progression in those with Babinski (diagnosis!!!) and in those with psychiatric side effects in first year of treatment with L-dopa therapy
<table>
<thead>
<tr>
<th>Study</th>
<th>Outcome measure</th>
<th>Results</th>
</tr>
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<tr>
<td>Maier Hoehn, 1983 (22)</td>
<td>HY</td>
<td>Disabled (HY stage IV or V) or dead; 1-5 disease 31/110 (28.1%), 6-10 disease 25/41 (61.0%), 11-15 disease 40/48 (83.3%), &gt;15 disease 17/19 (89.5%). Total patients observed 271-42 (cases first observed before 1949)-11 (lost to follow-up) = 229</td>
</tr>
<tr>
<td>Aimard, 1984 (21)</td>
<td>HY A=stadium I and II B= stadium III C = stadium IV and V</td>
<td>&lt; 3 years; A=68%; B=15%; C=17% &lt;br&gt; 3-6 years; A=46%; B=31%; C=23% &lt;br&gt; 6-10 years; A=28%; B=43%; C=29% &lt;br&gt; &gt; 10 years; A=39%; B=39%; C=22%</td>
</tr>
<tr>
<td>Guillard, 1986 (37)</td>
<td>Time to loss of independence</td>
<td></td>
</tr>
<tr>
<td>Markham, 1986 (27)</td>
<td>UCLA-scale HY</td>
<td>Baseline 22.4 (6.73) in group of 19; 104.0 (25.4) in group of 6 &lt;br&gt; Baseline 2 in group of 19; Follow-up 3.5 in group of 6</td>
</tr>
<tr>
<td>Goetz, 1988 (40)</td>
<td>Progression to HY III</td>
<td>The mean duration of symptoms until the rapidly progressive group progressed to HY III was 24.3 months</td>
</tr>
<tr>
<td>Diamond, 1989 (26)</td>
<td>UCLA-scale</td>
<td>Before L-dopa treatment L-dopa treatment no significant difference between men and women for the UCLA disability score; the first 3 years after L-dopa treatment no difference in UCLA disability score; after 3 years statistically significant difference in UCLA disability score between age at onset group &gt;60 and the other 2 groups</td>
</tr>
<tr>
<td>Diamond, 1990 (25)</td>
<td>UCLA-scale</td>
<td>Before L-dopa treatment and after L-dopa treatment no significant difference between men and women for the UCLA disability score</td>
</tr>
<tr>
<td>Chia, 1992 (24)</td>
<td>HY</td>
<td>At baseline: I 81, II 91, III 32, IV 10, V 1 &lt;br&gt; At follow-up: I 1, II 53, III 73, IV 62, V 26</td>
</tr>
<tr>
<td>Di Rocco, 1996 (29)</td>
<td>Time in months to progress to a successive stage of the HY scale</td>
<td>Stage 0-I 15.8 months, stage I-II 26.8 months, stage II-III 34.7 months, stage III-IV 48.5 months, IV-V 21.3 months</td>
</tr>
<tr>
<td>Ferraz, 1996 (39)</td>
<td>HY</td>
<td>No difference between rural and urban living group for getting better/worse over time as measured by Hoehn and Yahr</td>
</tr>
<tr>
<td>Mitchell, 1996 (9)</td>
<td>Own developed ADL-score ADL</td>
<td>Baseline 15, 6 months 15.75, 12 months 16.6, 18 months 17.5 &lt;br&gt; (functional dependence: 0-10 mild, 10-20 moderate, 20-30 severe)</td>
</tr>
<tr>
<td></td>
<td>UPDRS total score</td>
<td>Baseline: Total UPDRS 27.1 (13) &lt;br&gt; Year 3: Total UPDRS 22.6 (11) &lt;br&gt; Year 5: Total UPDRS 29.5 (13.8)</td>
</tr>
</tbody>
</table>
Prognostic factors

- Faster progression with akinetic-rigid subtype or severe kinesia at the start of L-dopa therapy and poor clinical result of L-dopa after 1 year (diagnosis!!!!)
- Higher age at onset associated with faster progression to HY III
- Younger age at onset favorable prognosis
- No difference in prognosis between men and women
- Not described in RR/OR; with 8-9 years of illness tremor at start and unilateral start of symptoms are a prognostic factor for less severe disability (stage IV and V) or dead when compared with other then tremor symptoms at start and bilateral onset respectively
- Age at onset did not correlate with clinical deterioration at the final visit
Table 2C. Results of observational studies on the course of perceived quality of life and its prognostic factors in patients with Parkinson’s disease

<table>
<thead>
<tr>
<th>Study</th>
<th>Outcome measure</th>
<th>Results</th>
</tr>
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<tbody>
<tr>
<td>Karlsen, 2000 (32)</td>
<td>NHP</td>
<td>NHP proportion with more than 30% increase in score = 58.6%; mean change score 56.0 (SD 110.8)</td>
</tr>
<tr>
<td>Marras, 2004 (34)</td>
<td>EQ-5D and VAS from EuroQol</td>
<td>No significant change in QoL between 0-4 years of follow-up</td>
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</tbody>
</table>

UPDRS = Unified Parkinson’s Disease Rating Scale; NHP= Nottingham Health Profile; QoL = Quality of Life; SD = Standard Deviation; grey cells mean high quality study.
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<th>Results</th>
<th>Prognostic factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Karlsen, 2000 (32)</td>
<td>NHP</td>
<td>NHP proportion with more than 30% increase in score = 58.6%; mean change score 56.0 (SD 110.8)</td>
<td>The authors could not identify any factors that could predict change in decreased QoL as measured by the increased NHP scores</td>
</tr>
<tr>
<td>Marras, 2004 (34)</td>
<td>EQ-5D and VAS from EuroQol</td>
<td>No significant change in QoL between 0-4 years of follow-up</td>
<td>Treatment regimen or motor complications are not related to lower QoL; dyskinesias in the first two years of treatment (and follow-up) are associated with better QoL scores (even when corrected for difference in UPDRS-scores); this correlation disappears in the last 2 years of follow-up</td>
</tr>
</tbody>
</table>

UPDRS = Unified Parkinson’s Disease Rating Scale; NHP = Nottingham Health Profile; QoL = Quality of Life; SD = Standard Deviation.
Reference List


Appendix 1. Specification of criteria list systematic review of the progression of PD and its prognostic factors.

Study population
A. Selection of study population
   Positive if study population consists of a consecutive sample, assembled at a common early point in the disease.
B. Description of inclusion and exclusion criteria
   Positive if criteria are formulated for at least:
   - Number of years since diagnosis/symptoms of Parkinson’s disease
   - Defined diagnosis of Parkinson’s disease according to Gelb (Gelb, 1999) or the UK Parkinson’s disease Society Brain Bank (Hughes, 1992); or in older studies description of relevant signs for the diagnosis (tremor/bradykinesia/rigidity/postural reflex abnormality) combined with the absence of signs (e.g. Babinski sign/Ataxia/early dementia/early autonomic features).
C. Baseline demographic and clinical characteristics are described for all subjects
   Positive if age, gender, age at onset, Modified Hoehn and Yahr and UPDRS, at least motor examination, are described.
D. Treatment subsequent to inclusion in cohort reported
   Positive if treatment is described.

Study size
E. Study size
   Positive if the number of patients included in the study is \( \geq 100 \).

Follow Up
F. Follow-up \( \geq 24 \) months
   Positive if the follow-up period is 24 months or more.
G. Drop-outs/loss to follow-up \( \leq 15\% \) or \( 20\% \)
   Positive if total number of drop-outs/loss to follow-up is smaller or equal to 15\% with one year follow-up; and positive if smaller or equal to 20\% with two or more years follow-up.
H. Information completers versus drop-outs/loss to follow-up
   Positive if demographic/clinical information is presented for completers and for drop-outs/loss to follow-up.

Outcome Measures
I. Relevance, validity and reproducibility of outcome measures
   Positive if at least 1 of the following 4 items are used as outcome measures: impairment, perceived disability in physical activities or performance in physical activities, quality of life, survival and if the study tested the validity/reproducibility of or referred to other studies in which validity/reproducibility of this outcome measure was established.

Prognostic factors
J. Description of potential prognostic factors
   Positive if at least the following factors are reported at baseline: age, sex, age at onset motor symptoms, physical impairment (tremor/bradykinesia/rigidity); including details of measurement (reliability/validity) if relevant.

Analysis and data presentation
K. Description of most important outcome measures
   Positive if, frequency/percentage/mean (SD/CI/Range) of at least 1 of the following 4 outcome measures are used for each follow-up measurement: impairment, perceived disability in physical activities or performance in physical activities, quality of life, survival.
L. Description of most important prognostic factors
   Positive if, frequency/percentage/mean (SD/CI/Range) of the most important prognostic factors are reported for each follow-up measurement.
M. Univariate technique
   Positive if univariate crude estimates are provided.
N. Multivariate technique
   Positive if appropriate multivariate techniques are used to adjust for other prognostic factors and adequate sample size (N) in relation to number of prognostic factors (K) (at least N:K=10:1)
### Appendix 2. Levels of evidence that were applied in the qualitative data analysis.

<table>
<thead>
<tr>
<th>Levels of Evidence</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strong evidence</td>
<td>Generally consistent findings in multiple high-quality cohort studies</td>
</tr>
<tr>
<td>Moderate evidence</td>
<td>Generally consistent findings in one high-quality cohort study and two or more high-quality case control studies, or in three or more high-quality case-control studies</td>
</tr>
<tr>
<td>Limited evidence</td>
<td>(Generally consistent) findings in a single high-quality cohort study, or in two or fewer high-quality case-control studies</td>
</tr>
<tr>
<td>Conflicting evidence</td>
<td>Conflicting findings in high-quality studies</td>
</tr>
<tr>
<td></td>
<td>(i.e. &lt;75% of the studies reported consistent findings)</td>
</tr>
<tr>
<td>No evidence</td>
<td>No high-quality studies could be found</td>
</tr>
</tbody>
</table>