Clinical Predictors of disease progression in Parkinson's disease

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Chapter 3:

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

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ABSTRACT

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

INTRODUCTION

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

METHODS

Study Design and Participants

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

Ascertainment of dementia

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

Assessment of Baseline Variables

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

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

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

Statistical analysis

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

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

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

Calculation of survival time

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

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

RESULTS

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

Cross-sectional analysis

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

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

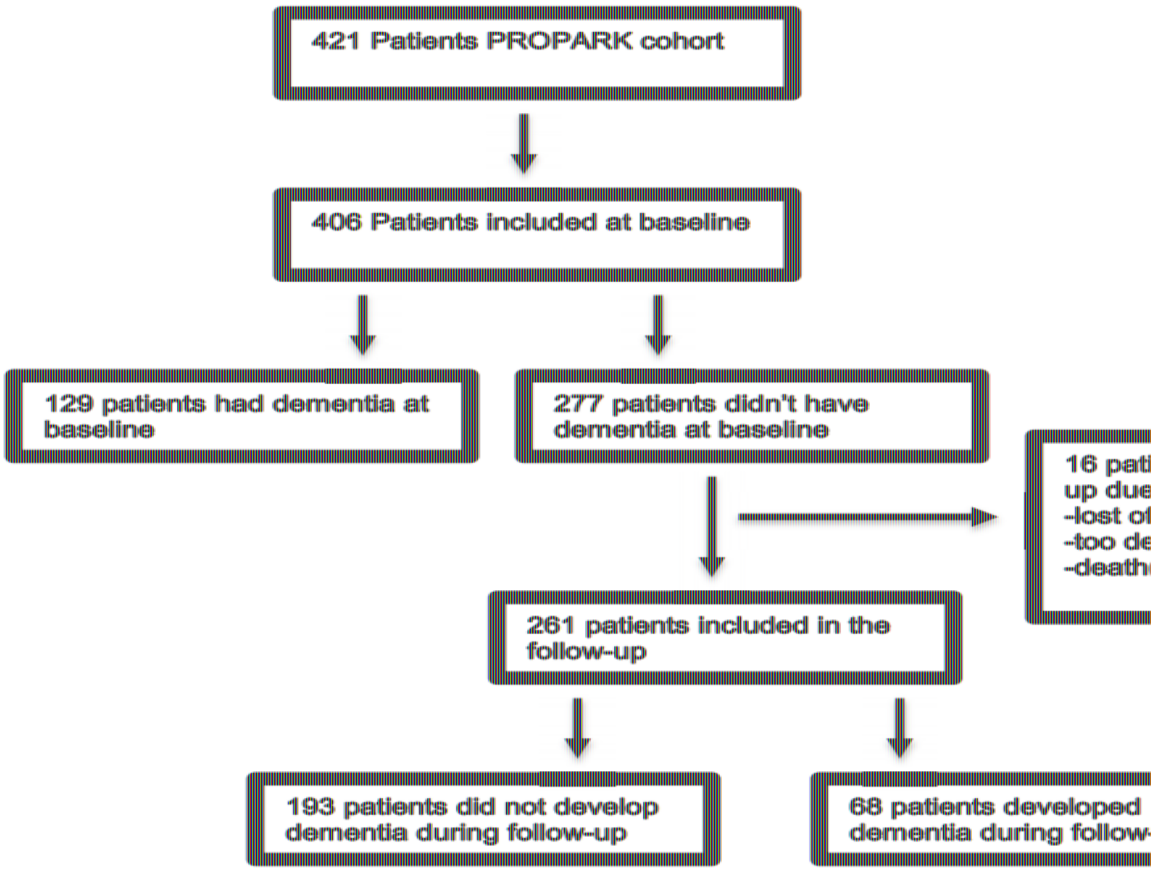
patients at baseline. In this analysis, the same variables were identified, except that dyskinesias and total LDE were not significant (Supplement 3.1, Table S3.1). In the multivariate analysis, age, education, depression and hallucinations were independently associated with the presence of dementia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

Table 3.1: Baseline data of patients with and without dementia

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

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

Figure 3.1: Flow Chart of follow-up for dementia



Longitudinal analysis

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

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

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

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

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

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

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

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

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

DISCUSSION

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

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

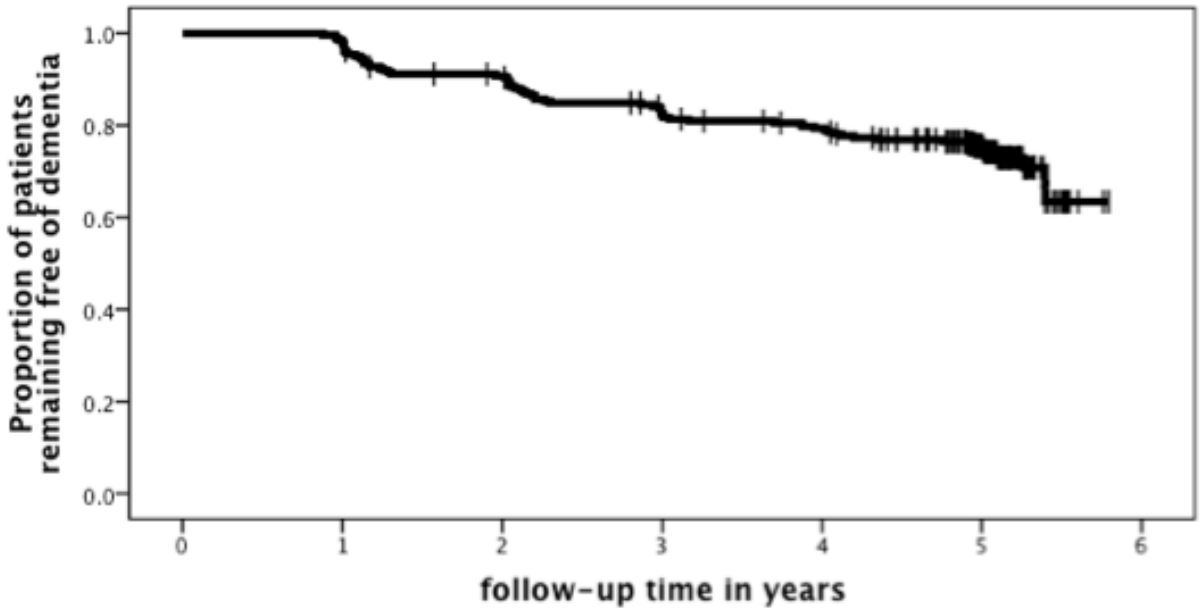
accumulation in the brainstem, basal forebrain regions, hypothalamus, and thalamus and accompanying neurochemical alterations in cholinergic, monoaminergic, dopaminergic, and histaminergic systems or the modulatory orexin/hypocretin systems.[38] Interestingly, similar neuroanatomical regions and neurotransmitter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

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

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

SUPPLEMENT 3.1

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



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

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

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

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

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

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

SUPPLEMENT 3.2

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

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

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

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

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

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