Postprint Version	1.0
Journal website	http://www.prd-journal.com/article/S1353-8020(15)30060-2/abstract
Pubmed link	https://www.ncbi.nlm.nih.gov/pubmed/26774535
DOI	10.1016/j.parkreldis.2015.12.007

The influence of age and approaching death on the course of nondopaminergic symptoms in Parkinson's disease

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ABSTRACT

Introduction: The influence of approaching death in addition to age and their interaction on the course of a broad spectrum of nondopaminergic features in Parkinson's disease (PD) has not been well studied.

This study addresses this issue in a prospectively designed study.

Methods: During five years, the severity of axial symptoms, cognitive impairment, psychotic symptoms, autonomic dysfunction, depressive symptoms, and daytime sleepiness was annually evaluated in PD patients. For each domain a linear mixed-effect model was used to examine changes during follow-up and relations with age and death.

Results: Of 378 included patients, 43 died during follow-up. Higher age was associated with increased severity of all nondopaminergic features except depression, and with a higher rate of progression of axial symptoms and cognitive impairment. Patients who died during follow-up had a higher severity of all nondopaminergic features except autonomic dysfunction, and a higher rate of progression of axial symptoms, cognitive impairment, and psychotic symptoms, compared to patients who survived.

Conclusion: This study shows that the severity of most nondopaminergic features and the progression rate of axial and psychotic symptoms and cognitive impairment increase before PD patients die, independent of the influence of age. An interaction between age and approaching death did not have a significant effect on the course of the symptoms. Improving our understanding of the fundamental biology underlying these factors and the interaction with factors intrinsic to the disease, may have profound implications for the treatment of PD.

1. INTRODUCTION

Parkinson's disease (PD) is a multi-system disorder characterized by features that occur as a consequence of degeneration of dopaminergic and nondopaminergic neurons [1]. Aging is the single most important risk factor for PD. In addition, age and age at onset are important determinants of disease progression, with patients with higher age and age at onset showing faster clinical progression [2]. Previously, the results of two studies on the PROPARK cohort showed a relation between six predominantly nondopaminergic domains (PND; i.e. axial motor features, cognitive decline, depression, psychotic symptoms, excessive daytime sleepiness, and autonomic dysfunction) and that these domains were strongly related to age [3,4].
A retrospective study using information from case records reported an exponential increase in severity of various PND features (including frequent falling, visual hallucinations and cognitive disability) in the final stage of PD, irrespective of the age at which death occurred [5,6]. Based on these results, the authors hypothesized that age influences the rate of progression especially in the early and middle stages of the disease, whereas in the period before death clinical progression is ruled by factors intrinsic to the disease process with little influence of age.
The influence of age and approaching death on the course of a broad spectrum of PND domains has not been studied comprehensively.
We addressed this issue by examining the influence of age, death and their interaction on the severity and progression of the aforementioned six PND domains using a prospectively designed study where data were annually collected in a standardized manner using valid and reliable instruments.

2. METHODS

2.1. Study design

The study is part of the “PROfiling PARKinson's disease” (PROPARK) study, a longitudinal cohort study of patients with PD, who are profiled on phenotype, genotype, disability and global outcomes of health, using valid and reliable assessment instruments for PD. Findings obtained from five consecutive annual assessments (baseline and four years follow-up) of 414 patients who were assessed between May 2003 and December 2009 were used for analyses. From the sixth annual assessment, only recordings of survival or death were taken into account.

2.2. Patients

All patients fulfilled the United Kingdom Parkinson's Disease Society Brain Bank (UKPDBB) criteria for idiopathic PD at each assessment [7]. Patients were recruited from outpatient neurology clinics of both university and regional hospitals in the western part of The Netherlands. The majority of the patients were assessed at the Leiden University Medical Center (LUMC); patients who were unable to come to the hospital were assessed at home. Since age at onset and disease duration are related to various manifestations of the disease, the recruitment strategy was to obtain an adequate distribution of these determinants within the cohort. A total of 100 patients were recruited in each of the four strata based on age at onset (_/> 50 years) and disease duration (_/> 10 years). Patients who had undergone stereotactic surgery were excluded since this intervention may significantly alter the natural course of the condition.

2.3. Standard protocol approvals, registrations, and patient consents

The studywas approved by the medical ethical committee of the LUMC and all patients gave written informed consent.

2.4. Measures

Measurement instruments for the different PND were derived from a prior project (Scales for Outcomes in PArkinson's disease: SCOPA) [8]. Outcomes of these measurement instruments are discrete sumscores referring to the severity of impairment in the domain. Axial symptoms (including the items rise, gait, and postural instability from the SPES/SCOPA-motor, range 0 -9), cognitive impairment (SCOPA-COG, range 0 -43), psychotic symptoms (SCOPA-PC, items 1 -5, range 0 -15), autonomic dysfunction (SCOPAAUT, items 4 -6, 8 -16, range 0 -36), depressive symptoms (Beck Depression Inventory (BDI), range 0 -63) and daytime sleepiness (DS) (SCOPA-SLEEP section DS, range 0 -18) were evaluated. Instruments were either self-completed (SCOPA-AUT, BDI, SCOPASLEEP) or administered by trained research associates (SCOPA-COG, SCOPA-PC, SPES/SCOPA). Scores of the SCOPA-COG were inversed to arrange that higher scores reflected more severe impairment in all domains. Age, age at onset (i.e. onset of first symptoms as perceived by the patient), disease duration, and disease severity (Hoehn and Yahr stage) [9] from the latest available assessment of the patient within the study period were used. Patients were recorded as deceased or survivor dependent on if they died or survived their period of study participation. Patients who deceased within 18 months after their last assessment were also recorded as deceased.
Patients who were lost during follow-up and patients who were known to be deceased but whose exact date of death could not be retrieved were excluded from the analyses. For reasons of comparability, all patients who used anti-parkinsonian medication were assessed while they benefited fromtheirmedication (i.e., were ‘on’). When exhaustion or off-periods were detected, patients were allowed to take a break or take medication. For each patient, a total levodopa equivalent (LDE) was calculated [10].

2.5. Statistics

For each nondopaminergic domain (axial, cognitive, psychotic, depressive and autonomic symptoms, and daytime sleepiness), linear mixed-effect models (LMM) were used to examine changes during the follow-up period and relations with covariates [11].
LMM take missing observations of the dependent variable into account under the assumption that the observations are missing at random. Since heterogeneity between patients was expected at baseline levels and for change of the clinical measurements over time, random intercepts and random slopes were used for the follow-up time in all models. Follow-up time in the LMM was modeled opposite to chronological time using years prior to the last observed assessment (last observed assessment in patients who survived or last assessment prior to death in patients who died).
This timeline made it possible to evaluate the influence of age, death and their interaction on the severity of symptoms closest to death or end of study.
Covariates were age at last assessment (standardized value), death during follow-up (y/n) and time, expressed as years to last assessment. The following interactions were included: time*age and time*death (to assess whether the covariates influenced the rate of change in the domain), age*death (to evaluate whether the influence of age

differed in patients who died or who survived), and the quadratic interactions age*age and time*time (to evaluate nonlinear influences of age and time). The following double interactions were included: age*death*time (to evaluate whether the influence of age on the rate of change in a domain differed between patients who died or who survived), time*time*age and time*- time*death (to assess if non-linear relations of time were influenced by age or death (i.e. accelerated increase in a domain score in time by higher/lower age or death/survival)), and age*age*time and age*age*death (to assess non-linear relations of age influenced by time or death (i.e. accelerated increase in severity by age influenced by time or by death/survival)). For each domain, the saturated model included the domain score as dependent variable and included all covariates and all interactions, and a random intercept and random slope with an unstructured covariance matrix. The saturated model was simplified by stepwise excluding the non-significant double interactions, and the non-significant interactions. The final model consists of all significant (double) interactions and all covariates. A p-value < 0.05 was considered statistically significant. For the double interaction a more stringent threshold of $p < 0.01$ was considered because of multiple testing. Analyses were performed using SPSS 17.0 (SPSS Inc, Chicago, IL, USA).

3. Results

Of the 414 patients that participated in the PROPARK study, 36 patients in total were excluded: 31 patients had undergone stereotactic surgery, 3 were lost to follow-up, and from 2 patients the exact date of death was unknown. In total, data of 1654 visits of 378 patients with a mean (SD) follow-up time of 3.44 (1.31) years were analyzed. Patients who died during follow-up (N ¼ 43) had 152 visits with a mean (SD) follow-up time of 2.62 (1.33) years.

Compared to patients who survived, patients who died were older (73.9 [SD 9.5] vs. 63.6 [SD 10.7]; $P < 0.0001$), had a higher age at onset (59.2 [SD 10.7] vs 50.1 [SD 11.3]; $P < 0.0001$), and more severe PD (H&Y 4 [IQR 4 -5] vs. H&Y 3 [IQR 2 -4]; $P < 0.0001$), whereas differences in disease duration and LDE were not significant (Table 1).

3.1. Axial symptoms

Older age was significantly associated with more severe axial symptoms. Patients who died during follow-up had significantly more axial symptoms compared to survivors. In all patients, the associations of axial symptoms with time, age and their interaction resulted in a non-linear deterioration over time, with a faster rate in older patients. The rate of deterioration was also faster in patients who died during follow-up than in survivors. Dying during followup had a larger influence on the rate of progression than having a 10 years older age than the average age (Fig. 1a; estimated regression coefficients: eTable 1 in supplement, first column).

3.2. Cognitive impairment

Older age was significantly associated with more severe cognitive impairment. Patients who died during follow-up had significantly more severe cognitive impairment than survivors. In survivors, the associations of cognitive impairment with time, age and their interactions showed a slight non-linear cognitive deterioration over time in older patients, whereas cognitive impairment remained nearly constant over time in average-aged and younger patients. Patients who died

during follow-up had a significantly faster rate of progression than survivors. Overall, the deterioration in cognitive scores was more pronounced in patients who died during follow-up than in survivors (Fig. 1b; estimated regression coefficients: eTable 1 in supplement, second column).

3.3. Psychotic symptoms

Older age and death were significantly related to more severe psychotic symptoms. Over time, all patients showed a significant linear deterioration, with a significantly faster rate for patients who died compared to the survivors. Age had no significant effect on the rate of progression of psychotic symptoms (Fig. 1c; estimated regression coefficients: eTable 1 in supplement, third column).

3.4. Depressive symptoms

Death during follow-up was significantly related to more severe depressive symptoms. Agewas not significantly associated with the severity of depressive symptoms. All patients showed a significant deterioration of depressive symptoms in the years prior to the last assessment, without differences between the different age groups or between patients who died or survived during follow-up (Fig. 1d; estimated regression coefficients: eTable 1 in supplement, fourth column).

[TABLE 1]

3.5. Autonomic symptoms

Older age was significantly associated with more severe autonomic symptoms, whereas death during follow-up was not. Autonomic symptoms showed a significant deterioration over time in the years prior to the last assessment, without differences in deterioration between the different age groups or between patients who died during follow-up and survivors (Fig. 1e; estimated regression coefficients: eTable 1 in supplement, fifth column).

3.6. Daytime sleepiness Older age and death during follow-up were significantly related to more severe daytime sleepiness. The association between age and daytime sleepiness was non-linear; the increase in severity diminished with older age. Over time, daytime sleepiness significantly deteriorated, without differences in deterioration between different age groups or between patients who died or survived during follow-up (Fig. 1f; estimated regression coefficients: eTable 1 in supplement, sixth column).

4. DISCUSSION

There is growing recognition of the role of PND domains across the entire disease course and of their importance as determinants of quality of life of PD patients [12]. Although a general effect of age on the rate of progression of symptoms in PD has been reported [13,14], a more nuanced view holds that age influences mainly the early and middle disease stages, whereas in the advanced disease stage with approaching death the features progress in a similar manner irrespective of age [5,6]. Since this latter hypothesis was based on findings derived from a retrospective analysis of case records, we evaluated the influence of age and approaching death on six important PND domains in a prospective study design.

We found that older age was associated with a higher severity of symptoms in all domains, except for depressive symptoms.

Compared to survivors, patients who died during follow-up had significantly more severe symptoms in all domains except for autonomic symptoms. In none of the domains the severity of symptoms was associated with an interaction between age and death.
As expected, all PND domains showed a significant increase in severity over time. Age and death during follow-up significantly increased the rate of progression of axial symptoms and cognitive impairment. For psychotic symptoms, the rate of progression was only increased in patients who died during follow-up; age had no effect on the progression rate of psychotic symptoms. Survivors in the average-aged and young age groups showed no deterioration in cognitive impairment over time. This finding could reflect a learning effect that is present in younger cases and diminishes as patients become older. In none of the domains, the interaction between age and death had an influence on the progression rate.

[FIGURE 1]

Our results are in line with other studies reporting old age as a predictor of cognitive decline, dementia or daytime sleepiness [14 -17], and those reporting more rapid cognitive decline in older patients [13]. The gradual worsening of these PND symptoms disease progresses [4,5,13,18 -20] is generally attributed to expanding Lewy body pathology across the nervous system [6,21].
In turn, the accumulating Lewy body pathology in the nervous system is a result of converging pathways that perturb critical functions (such as mitochondrial bioenergetics, protein quality and folding control, and oxido-reductive homeostasis) [22 -24]. These pathways enhance each other, and are likely potentiated by aging. As aging is intrinsically complex and affects multiple functions, the understanding of these dynamics are still limited [25]. Consequently, their detrimental consequences on degeneration of dopaminergic and nondopaminergic neurons in PD remain to be determined.
Studies that evaluated the final stage of PD, reported an increased risk of visual hallucinations, falls and dementia [5,6], and a higher rate of progression of motor symptoms (including gait and balance) in the period before death [26]. In our study, it turned out that the progression rate of exactly those domains that are comparable to the above-mentioned three symptoms (i.e., cognitive impairment, axial and psychotic symptoms) was influenced by death during follow-up. In the general population, the hypothesis of ‘terminal decline’ has been described [27]. Terminal decline has been mainly described as accelerated late life cognitive decline [27], but has also been noticed for motor dysfunction [28]. This deterioration is attributed to mortality related processes rather than the aging process. It has been argued that this phenomenon is a presentation of common diseases, like Lewy body disease, Alzheimer disease or cerebrovascular disease. In a clinicopathologic study on patients without known diseases it appeared that levels of plaques and tangles were associated with an earlier onset of terminal decline in motor and cognitive function. However, these measures did not explain the rate of terminal motor decline [28]. Another clinicopathologic study demonstrated that indices for these diseases can explain a part, but not all variation of late life cognitive decline [29]. Interestingly, a similar course of terminal cognitive decline was observed in other diseases including cancer, and coronary heart disease [30].

Surprisingly, we did not observe a significant relation between approaching death and severity or progression of autonomic dysfunction, while this domain was identified as a component of a coherency pattern together with the other five nondopaminergic domains evaluated in this study [3]. One explanation for this finding might be that the potential premotor involvement of autonomic dysfunction in PD limits its role to the early and middle stages of the disease.

The results of our study did not confirm an effect of interaction between age and approaching death on the severity or progression of PND domains. Although we did find an increase in the progression rate of cognitive dysfunction and axial and psychotic symptoms, we could not confirm the hypothesis of a non-linear or exponential curve of clinical progression unrelated to age during the period prior to death, nor the hypothesis that age has a more pronounced influence on the early and middle stage compared to the final stage of PD, as described by Kempster et al. [5,6] However, the limited number of data points per patient in our study may have precluded the detection of exponential associations.

Strengths of this study are the extensive four year follow-up measurements of six nondopaminergic domains in a large number of patients and the use of clinimetrically sound measurement instruments [8]. Potential limitations of this study concern the potential presence of a learning effect in the SCOPA-COG which may have precluded the identification of a subtle cognitive decline.

The length of the follow-up time may have been too short, which may have impeded the identification of certain patterns over time.

Furthermore, annual follow-up may not be frequent enough to observe symptoms such as psychosis that can progress rapidly in an advanced disease population.

Diagnoses of patients were not autopsy-confirmed, but re-evaluation of UKPDBB criteria occurred annually. The cohort stratification in our study resulted in a cohort that reflected a broad spectrum of the disease course; however, de novo patients and patients in the very advanced stages of the disease may have been underrepresented.

The relatively small number of patients who died during follow-up may have resulted in overlooking associations or interactions with approaching death.

Furthermore, since prevalent PD patients were included, there may be a confounding influence of treatment on the results. However, since nondopaminergic features are less susceptible to the influence of antiparkinsonian medication, this source of confounding likely played a minor role compared to studies which focused on dopaminergic features of the disease. However, medications specifically prescribed for a nondopaminergic symptom were not taken into account which can have an impact on clinical outcomes.

Overall, this study shows that age is an important determinant of the severity of most of the PND domains and of the progression of axial symptoms and cognitive dysfunction. Approaching death was associated with a higher severity of most PND symptoms and higher progression rate of cognitive dysfunction, axial impairment and psychotic symptoms. Our findings highlight the impact of factors associated with aging and those associated with approaching death on the severity and progression of PD. Thus, improving our understanding of the fundamental biology underlying these factors may have the potential to significantly impact upon the treatment of patients with PD.

Acknowledgments This study was funded by Prinses Beatrix Fonds (PBF, project no.

WAR05-0120), the van Alkemade-Keuls Foundation, and the Dutch Parkinson's disease Society. There was no involvement of the funding sources in study design, collection, analysis and interpretation, writing of the report, or the decision to submit the article for publication.

Appendix A. Supplementary data Supplementary data related to this article can be found at http:// dx.doi.org/10.1016/j.parkreldis.2015.12.007.

REFERENCES

[1] C. Marras, A. Lang, Invited article: changing concepts in Parkinson disease: moving beyond the decade of the brain, Neurology 70 (21) (2008) 1996e2003.
[2] J.V. Hindle, Ageing, neurodegeneration and Parkinson's disease, Age Ageing 39 (2) (2010) 156e161.
[3] S.M. van Rooden, M. Visser, D. Verbaan, J. Marinus, J.J. van Hilten, Patterns of motor and non-motor features in Parkinson's disease, J. Neurol. Neurosurg.
Psychiatry 80 (8) (2009) 846e850.
[4] S.M. van Rooden, F. Colas, P. Martinez-Martin, M. Visser, D. Verbaan, J. Marinus, et al., Clinical subtypes of Parkinson's disease, Mov. Disord. 26 (1) (2011) 51e58.
[5] P.A. Kempster, D.R. Williams, M. Selikhova, J. Holton, T. Revesz, A.J. Lees, Patterns of levodopa response in Parkinson's disease: a clinico-pathological study, Brain 130 (Pt 8) (2007) 2123e2128.
[6] P.A. Kempster, S.S. O'Sullivan, J.L. Holton, T. Revesz, A.J. Lees, Relationships between age and late progression of Parkinson's disease: a clinicopathological study, Brain 133 (Pt 6) (2010) 1755e1762.
[7] W.R. Gibb, A.J. Lees, The relevance of the Lewy body to the pathogenesis of idiopathic Parkinson's disease, J. Neurol. Neurosurg. Psychiatry 51 (6) (1988) 745e752.
[8] www.scopa-propark.eu.
[9] M.M. Hoehn, M.D. Yahr, Parkinsonism: onset, progression and mortality, [10] R.A. Esselink, R.M. de Bie, R.J. de Haan, M.W. Lenders, P.C. Nijssen, M.J. Staal, et al., Unilateral pallidotomy versus bilateral subthalamic nucleus stimulation in PD: a randomized trial, Neurology 62 (2) (2004) 201e207.
[11] G.M. Fitzmaurice, N.M. Laird, J.H. Ware, Applied Longitudinal Analysis, Wiley-Interscience, Hoboken, N.J., 2004.
[12] P. Martinez-Martin, C. Rodriguez-Blazquez, M.M. Kurtis, K.R. Chaudhuri, The impact of non-motor symptoms on health-related quality of life of patients with Parkinson's disease, Mov. Disord. 26 (3) (2011) 399e406.
[13] D. Aarsland, K. Andersen, J.P. Larsen, R. Perry, T. Wentzel-Larsen, A. Lolk, et al., The rate of cognitive decline in Parkinson disease, Arch. Neurol. 61 (12) (2004) 1906e1911.
[14] C.H. Williams-Gray, J.R. Evans, A. Goris, T. Foltynie, M. Ban, T.W. Robbins, et al., The distinct cognitive syndromes of Parkinson's disease: 5 year follow-up of the CamPaIGN cohort, Brain 132 (Pt 11) (2009) 2958e2969.
[15] M.D. Gjerstad, G. Alves, T. Wentzel-Larsen, D. Aarsland, J.P. Larsen, Excessive daytime sleepiness in Parkinson disease: is it the drugs or the disease? Neurology 67 (5) (2006) 853e858.
[16] T.A. Hughes, H.F. Ross, S. Musa, S. Bhattacherjee, R.N. Nathan, R.H. Mindham, et al., A 10-year study of the incidence of and factors predicting dementia in Parkinson's disease, Neurology 54 (8) (2000) 1596e1602.
[17] C.H. Williams-Gray, T. Foltynie, C.E. Brayne, T.W. Robbins, R.A. Barker, Evolution of cognitive dysfunction in an incident Parkinson's disease cohort, Brain 130 (Pt 7) (2007) 1787e1798.
[18] M.A. Hely, J.G. Morris, W.G. Reid, R. Trafficante, Sydney multicenter study of Parkinson's disease: non-L-dopa-responsive problems dominate at 15 years, Mov. Disord. 20 (2) (2005) 190e199.
[19] P. Hobson, W. Islam, S. Roberts, V. Adhiyman, J. Meara, The risk of bladder and autonomic dysfunction in a community cohort of Parkinson's disease patients and normal controls, Park. Relat. Disord. 10 (2) (2003) 67e71.

[20] O. Riedel, I. Heuser, J. Klotsche, R. Dodel, H.U. Wittchen, Occurrence risk and structure of depression in Parkinson disease with and without dementia: results from the GEPAD Study, J. Geriatr. Psychiatry Neurol. 23 (1) (2010) 27e34.
[21] W.D. van de Berg, D.H. Hepp, A.A. Dijkstra, J.A. Rozemuller, H.W. Berendse, E. Foncke, Patterns of alpha-synuclein pathology in incidental cases and clinical subtypes of Parkinson's disease, Park. Relat. Disord. 1 (18 Suppl) (2012) S28eS30.
[22] D. Ebrahimi-Fakhari, L. Wahlster, P.J. McLean, Protein degradation pathways in Parkinson's disease: curse or blessing, Acta Neuropathol. 124 (2) (2012) 153e172.
[23] M.P. Horowitz, C. Milanese, M.R. Di, X. Hu, L.M. Montero, L.H. Sanders, et al., Single-cell redox imaging demonstrates a distinctive response of dopaminergic neurons to oxidative insults, Antioxid. Redox Signal. 15 (4) (2011) 855e871.
[24] W. Xie, O.W. Wan, K.K. Chung, New insights into the role of mitochondrial dysfunction and protein aggregation in Parkinson's disease, Biochim. Biophys.
Acta 1802 (11) (2010) 935e941.
[25] B.A. Yankner, T. Lu, P. Loerch, The aging brain, Annu. Rev. Pathol. 3 (2008) 41e66.
[26] E.D. Louis, M.X. Tang, L. Cote, B. Alfaro, H. Mejia, K. Marder, Progression of parkinsonian signs in Parkinson disease, Arch. Neurol. 56 (3) (1999) 334e337.
[27] D. Gerstorf, N. Ram, Inquiry into terminal decline: five objectives for future study, Gerontologist 53 (5) (2013) 727e737.
[28] R.S. Wilson, E. Segawa, A.S. Buchman, P.A. Boyle, L.P. Hizel, D.A. Bennett, Terminal decline in motor function, Psychol. Aging 27 (4) (2012) 998e1007.
[29] P.A. Boyle, R.S. Wilson, L. Yu, A.M. Barr, W.G. Honer, J.A. Schneider, et al., Much of late life cognitive decline is not due to common neurodegenerative pathologies, Ann. Neurol. 74 (3) (2013) 478e489.
[30] B.J. Small, L. Fratiglioni, S.E. von, L. Backman, Terminal decline and cognitive performance in very old age: does cause of death matter? Psychol. Aging 18 (2) (2003) 193e202.

TABLES AND FIGURES

Table 1
Characteristics of patients at their last assessment.

	Total group	Patients who survived during follow-up	Patients who died during follow-up	P-value
N (%)	378 (100)	335 (89)	43 (11)	–
Men, n (%)	242 (64)	211 (63)	31 (72)	0.3160[a]
Age, years	64.7 (11.0)	63.6 (10.7)	73.9 (9.5)	<0.0001[b]
Age at onset, years	51.2 (11.6)	50.1 (11.3)	59.2 (10.7)	<0.0001[b]
Disease duration, years	13.6 (6.1)	13.4 (6.2)	14.7 (5.3)	0.2078[b]
H&Y stage, median (IQR)	3 (2–4)	3 (2–4)	4 (4–5)	<0.0001[c]
LDE, mg/day	837.5 (831.2)	817.5 (713.9)	993.1 (1456.1)	0.1925[b]

Means (sd) are presented unless stated otherwise.
H&Y: Hoehn and Yahr stage, IQR: Interquartile range, LDE: Levodopa dose equivalent.
[a] Yates corrected Chi-square test.
[b] Student's t-test for independent samples.
[c] Mann–Whitney U test.

Rooden, S.M. van, Verban, D., Stijnen, T., Marinus, J., Hilten, J.J. van. The influence of age and approaching death on the course of nondopaminergic symptoms in Parkinson's disease. Parkinsonism & Related Disorders: 2016, 24(3), 113-118

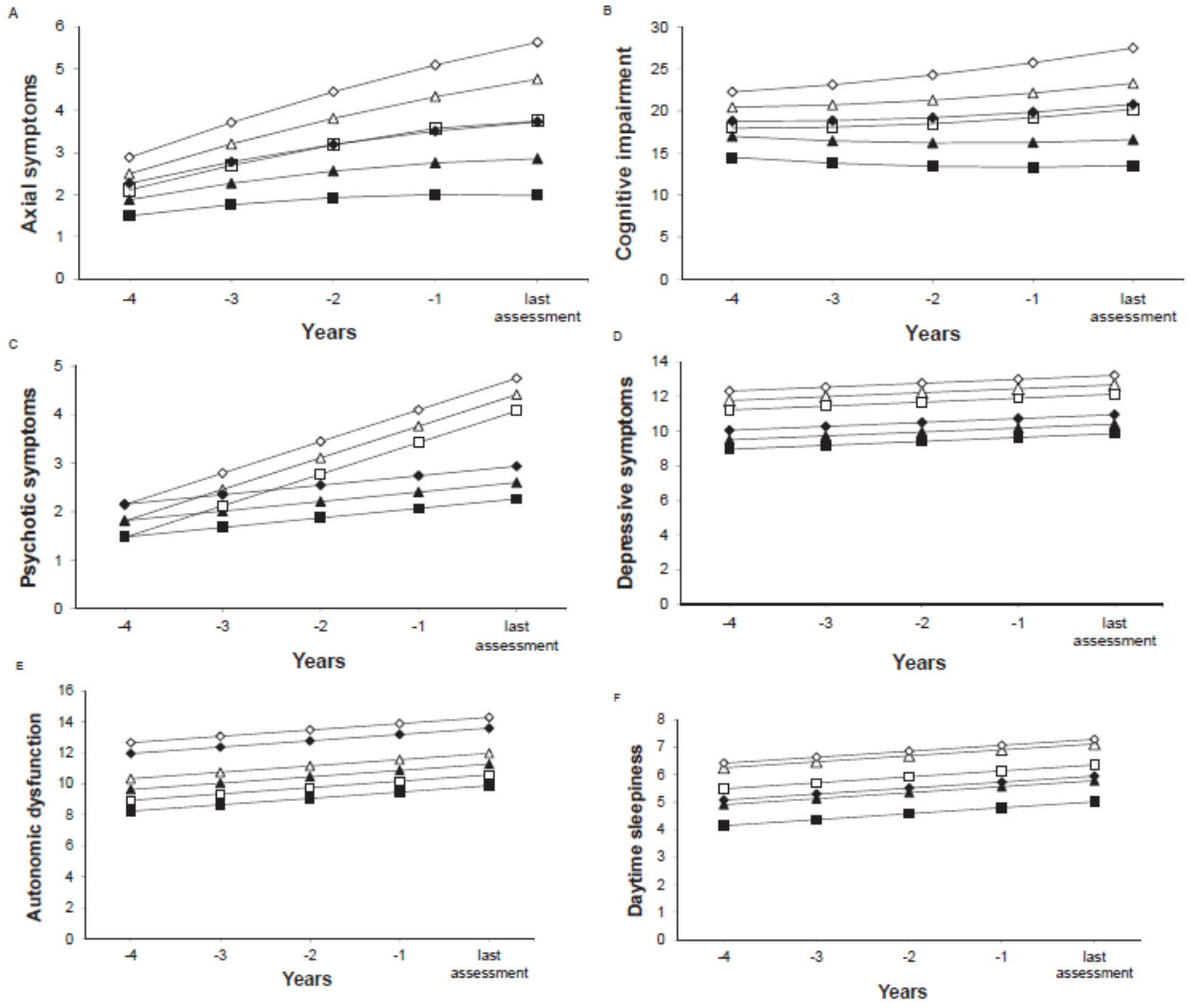

Fig. 1. A–F Course of nondopaminergic domains, from up to four years prior to last assessment until last assessment.
■: patients who survived with average age − 10 years.
□: patients who died with average age − 10 years.
▲: patients who survived with average age.
△: patients who died with average age.
◆: patients who survived with average age + 10 years.
◊: patients who died with average age + 10 years.
Profiles are presented for patients who died or who survived during follow-up with sample average age (64.8 years), with sample average age + 10 years (74.8 years), and with sample average age − 10 years (54.8 years). The profiles are presented in chronological order, but in reversed order compared to the statistical models. All patients had a last assessment (either before death or before the end of study) and a maximum of 4 years prior to this last assessment. The coefficients are estimated with linear mixed-effect models.