

Trajectories of prediagnostic functioning in Parkinson's disease

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At the time of clinical diagnosis, patients with Parkinson's disease already have a wide range of motor and non-motor features that affect their daily functioning. However, the temporal sequence of occurrence of these features remains largely unknown. We studied trajectories of daily functioning and motor and non-motor features in the 23 years preceding Parkinson's disease diagnosis by performing a nested case-control study within the prospective Rotterdam study. Between 1990 and 2013, we repeatedly performed standardized assessments of daily functioning (Stanford Health Assessment Questionnaire, Lawton Instrumental Activities of Daily Living Scale), potential prediagnostic motor (hypo- and bradykinesia, tremor, rigidity, postural imbalance, postural abnormalities) and non-motor features of Parkinson's disease, including cognition (Mini-Mental State Examination, Stroop Test, Letter-Digit-Substitution Test, Word Fluency Test), mood (Center for Epidemiological Studies-Depression Scale, Hamilton Anxiety and Depression Scale), and autonomic function (blood pressure, laxative use). In addition, the cohort was followed-up for the onset of clinical Parkinson's disease using several overlapping modalities, including repeated in-person examinations, as well as complete access to medical records and specialist letters of study participants. During follow-up, 109 individuals were diagnosed with Parkinson's disease, and each case was matched to 10 controls based on age and sex (total $n = 1199$). Subsequently, we compared prediagnostic trajectories of daily functioning and other features between Parkinson's disease cases and controls. From 7 years before diagnosis onwards, prediagnostic Parkinson's disease cases more commonly had problems in instrumental activities of daily functioning, and more frequently showed signs of movement poverty and slowness, tremor and subtle cognitive deficits. In the past 5 years, Parkinson's disease cases developed additional motor features (postural imbalance, rigidity, and postural abnormalities) and increasingly reported problems in basic daily activities. Parkinson's disease cases also increasingly reported anxiety symptoms, depressive symptoms, and use of laxatives throughout study follow-up, although differences with controls only became statistically significant in the last years before diagnosis. In conclusion, in patients with prediagnostic Parkinson's disease, impairments in instrumental daily activities, which require both motor and non-motor skills, pre-date difficulties in more physically oriented daily activities.

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Abbreviations: BADL = Basic Activities of Daily Living; IADL = Instrumental Activities of Daily Living; LDST = Letter Digit Substitution Test; MMSE = Mini-Mental State Examination; WFT = Word Fluency Test

Introduction

Although primarily characterized by a set of motor symptoms known as parkinsonism, patients with early clinical Parkinson's disease may present with various features that affect daily functioning well beyond impaired motor function, such as mild cognitive impairment, depressive symptoms, and mild autonomic dysfunction (Lees *et al.*, 2009; de la Riva *et al.*, 2014). To date, no therapies have been shown to modify disease progression in patients with Parkinson's disease, which may be a consequence of the advanced stage of pathology that early clinical Parkinson's disease patients already have (Lang *et al.*, 2013). Therefore, there is growing interest in defining earlier stages of the disease.

Over seven decades ago, it was already recognized that a proportion of patients who went on to be diagnosed with Parkinson's disease had prodromal symptoms (Kinnier Wilson, 1940). This observation was later corroborated by a case study of professional soccer player Ray Kennedy, who had presented with prodromal symptoms years before Parkinson's disease diagnosis, including motor symptoms 7 years before diagnosis (Lees, 1992). A Dutch case-control study subsequently identified CNS, psychological, musculoskeletal, and autonomic symptoms in patients with prediagnostic Parkinson's disease (Gonera *et al.*, 1997). More recently, a registry-based study showed that in the 10 years preceding clinical diagnosis a range of motor and non-motor features become increasingly prevalent in patients with Parkinson's disease (Schrag *et al.*, 2015). However, to date, no study has been published on long-term trajectories of prediagnostic features using data that were repeatedly and consistently assessed in both Parkinson's disease patients and controls. Furthermore, patterns of deterioration in various motor, limbic, autonomic, and cognitive features of Parkinson's disease have not yet been explored systematically. Insight into these trajectories, and their combined effects on daily functioning, could possibly aid in earlier diagnosis of Parkinson's disease and contribute to the identification of subjects who would benefit from early symptomatic treatment. Moreover, it may inform clinical studies on which subjects may be most suitable for inclusion in neuroprotective trials.

Within the prospective Rotterdam Study, we used repeated assessments to investigate differences in prediagnostic trajectories of patients with Parkinson's disease and control subjects.

Materials and methods

Setting

The study was embedded in the Rotterdam Study, a large, prospective, population-based cohort study in the Netherlands (Hofman *et al.*, 1991, 2015). The study was initiated in 1990, inviting all inhabitants of Ommoord aged ≥ 55 years; 7983 participants (78%) agreed to participate. At baseline, participants were screened for parkinsonism and dementia. For this report, we excluded subjects with prevalent parkinsonism or dementia or an unknown status of either, leaving 6456 subjects at risk of Parkinson's disease.

We monitored participants for the development of Parkinson's disease from baseline until first of: parkinsonism, dementia, death or 1 January 2013. Until 2013, the study has had a total of five visits, including four follow-up visits between 1993–95, 1997–99, 2002–04, and 2009–11. At each visit, participants undergo home interviews and medical examinations at the research centre. We studied daily functioning as well as motor and non-motor features that were measured at least at three different visits, except for anxiety, which was only measured at two visits. An overview of the assessed features is presented in Table 1 and additional details on assessment moments are presented in Supplementary Table 1. Study follow-up for Parkinson's disease was virtually complete.

Study design and study population

This study consists of a matched nested case-control sample from the Rotterdam Study. The overall age- and sex-adjusted incidence rate of Parkinson's disease in the Rotterdam Study is 1.5 per 1000 person-years (Darweesh *et al.*, 2016a) and age-specific incidence rates are somewhat higher than in most other population-based studies (de Lau and Breteler, 2006). Fifty-nine per cent of participants in this cohort are female (Darweesh *et al.*, 2016b).

All participants diagnosed with Parkinson's disease during follow-up were included as cases, if they met the following criteria: (i) were non-demented and had no parkinsonism (Parkinson's disease or parkinsonism due to other causes) at the baseline visit; (ii) were not diagnosed with dementia before Parkinson's disease diagnosis; (iii) were not diagnosed with parkinsonism due to other causes; and (iv) they participated at the visit before Parkinson's disease diagnosis. Participants used as controls had to have the following characteristics: (i) they were non-demented and had no Parkinson's disease at baseline visit; (ii) were free of parkinsonism and dementia at the time of diagnosis of the matched Parkinson's disease case; (iii) participated at the visit before diagnosis of the

Table 1 Overview of potential prediagnostic features of Parkinson's disease in the Rotterdam Study

Group	Feature	Test(s)	Interpretation	
Motor features	Hypo- and/or bradykinesia	Arm swing (L/R)	0. Normal; 2. Reduced	
		Gait	0. Normal; 1. Shuffling/small steps; 2. Propulsion + festination	
		General impression of hypo- and bradykinesia	0. Normal; 1. Less spontaneous movement; 2. Clear movement poverty or slowness	
	Tremor	Finger tapping (L/R)	0. Normal; 1. Somewhat slowed down /lower amplitude; 2. Slowed down	
		Resting tremor (L/R)	0. No; 1. Doubtful; 2. Yes	
		Intention tremor (L/R)		
	Rigidity	Positional tremor (L/R)		
	Postural balance	Tone arm (L/R)	0. Normal; 1. Raised	
Postural abnormalities	Maintain standing balance in steady stance in response to external perturbation	0. Normal; 1. Doubtful; 2. Impaired		
	General impression of posture	0. Fitting age; 1. Head/neck/arms flexed; 2. Kyphosis and arms/legs flexed		
Non-motor features	Falling	Questionnaire/self-reported fall in the previous 12 months	0. No; 1. Yes	
		Cognition: objective	MMSE	0–30 points
			Stroop test tasks 1–3	Number of seconds needed to finish the task
	Letter-Digit-Substitution Test		Number of correct letter-digit combinations in 60 s	
	Cognition: subjective	Word Fluency Test	Number of animals correctly named in 60 s	
		Memory complaints (3 items)	0. No; 1. Yes	
	Depressive symptoms	Center for Epidemiological Studies - Depression Scale (CES-D; 20 items)	0–60 points	
		Anxiety symptoms	Hamilton Anxiety and Depression Scale (HADS; anxiety subscale)	0–21 points
	Daily functioning	Hypotension	Systolic & diastolic blood pressure	Continuous scale (mm Hg)
		Constipation	Self-reported laxative use	0. No; 1. Yes
Daily functioning	BADL	Stanford Health Assessment Questionnaire (20 items)	8 component scores and overall score	
	IADL	Instrumental Activities of Daily Living scale (8 items)	8 component scores and overall score	

matched Parkinson's disease case; and (iv) were matched to a Parkinson's disease case by age (± 3 years) and sex. We matched 10 controls for every Parkinson's disease case at follow-up, resulting in inclusion of 109 Parkinson's disease cases and 1090 controls (total $n = 1199$). Due to missing data on some features, numbers of participants may vary across individual analyses.

Ascertainment of parkinsonism and Parkinson's disease

At baseline, we used a two-phase design to identify subjects with parkinsonism or Parkinson's disease, which was previously described in detail (de Rijk *et al.*, 1995; Darweesh *et al.*, 2016a). In short, all participants were first screened at the research centre for signs of parkinsonism, and individuals who screened positive received a structured clinical work-up (Unified Parkinson's Disease Rating Scale, UPDRS) by a research physician specialized in neurological disorders to establish parkinsonism. We obtained additional information from medical records of specialists and general practitioners. Persons who were suspected of having Parkinson's disease were further evaluated by an experienced neurologist.

During follow-up, we used four overlapping modalities to screen for potential parkinsonism: in-person screening and

interviews during centre visits (on average every 4 years), use of anti-parkinson medication, and alerts from continuous monitoring of clinical records (de Lau *et al.*, 2004; Darweesh *et al.*, 2016a). We did not have complete data on each modality for each participant, but the proportion of complete data for each modality was very high: on average 93% per centre visit round, and 99% for medical and pharmacy records (Clark *et al.*, 2002). Persons who screened positive in any of these methods were invited for a UPDRS examination by a research physician specialized in neurological disorders to establish parkinsonism. In addition, of all subjects who screened positive, complete medical records were studied and case reports were drawn up covering all potentially relevant information to establish presence and cause of parkinsonism. These case reports were evaluated by a panel led by an experienced neurologist, and the neurologist made the definitive diagnosis. In the process of establishing a diagnosis of parkinsonism, the neurologist did not have access to data on risk factors that were routinely assessed in all Rotterdam Study participants.

Parkinsonism was defined as at least one of: (i) the presence of hypo- or bradykinesia in combination with at least one other cardinal sign (resting tremor, rigidity or postural imbalance) as observed by any physician; or (ii) a clinical diagnosis of parkinsonism by a neurologist or geriatrician. To ensure that there were no parkinsonism cases in the control group,

we further considered a clinical diagnosis of parkinsonism by other physicians as possible parkinsonism; however, these subjects were not considered Parkinson's disease cases.

Parkinson's disease was diagnosed after exclusion of parkinsonism associated with pre-existent dementia, use of anti-dopaminergic drugs, cerebrovascular disease, multiple system atrophy, progressive supranuclear palsy, and evidence for other rare causes (e.g. corticobasal degeneration), in subjects with at least one of: (i) a clinical Parkinson's disease diagnosis by a neurologist or geriatrician; (ii) positive response to dopaminergic treatment; or (iii) DAT-scan findings consistent with Parkinson's disease. Subjects with parkinsonism who did not fulfil Parkinson's disease criteria were considered secondary parkinsonism cases.

After initial diagnosis, medical records of all incident parkinsonism cases (both Parkinson's disease and secondary) continued to be scrutinized until the end of the study period for new information that could lead to a revision of the diagnosis. Person-time at risk for incident Parkinson's disease ended at the first of the following: diagnosis of incident parkinsonism (due to either Parkinson's disease or other causes), incident dementia, death or 1 January 2013.

Ascertainment of dementia

Participants were screened for dementia at baseline and follow-up examinations using a three-step protocol (Schrijvers *et al.*, 2012), comprising two brief tests of cognition [Mini-Mental State Examination (MMSE) and Geriatric Mental State schedule (GMS) organic level (Folstein *et al.*, 1975; Copeland *et al.*, 1976)]. Individuals with positive screen results then underwent the Cambridge Examination for Mental Disorders of the Elderly (Roth *et al.*, 1986). Additional information was obtained from in-person examination by a neuropsychologist, clinical monitoring and neuroimaging. A consensus panel, led by an experienced neurologist, decided on the final diagnosis in accordance with standard criteria using the DSM-III-R criteria for dementia.

Preclinical features investigated

We considered various putative features of Parkinson's disease that have been implicated during the prediagnostic phase of the disease. These features were grouped into daily functioning, motor features, and non-motor features. This is also the order that we use to describe ascertainment methods and present results.

Daily functioning

Functioning in Basic Activities of Daily Living (BADL) was assessed using the disability index of the Stanford Health Assessment Questionnaire (Fries *et al.*, 1982). The questionnaire consists of 20 items constituting eight components: activities, arising, dressing and grooming, eating, hygiene, grip, reach, and walking. In our study, two of three items of eating (ability to cut meat and drink a glass of milk) were combined into one. All items could be scored from 0 to 3, with higher scores reflecting worse ability: 0 = no difficulty, 1 = some difficulty, 2 = much difficulty, and 3 = unable to. Component scores were calculated as the highest scored item

belonging to the respective component. Subsequently, BADL was calculated as the sum of the eight components.

Functioning in Instrumental Activities of Daily Living (IADL) was assessed using the IADL scale (Lawton and Brody, 1969). The IADL scale consists of eight items: shopping, washing, travelling on your own, finance management, phoning, medication use, housekeeping, and meal preparation. Similar to BADL, items were coded from 0 to 3, with higher scores reflecting worse ability. For IADL, items scored as non-applicable were imputed using the mean of five imputations, based on age, sex, scores on BADL items, and scores on other IADL items. Imputation of non-applicable values has been suggested and implemented by previous studies to prevent loss of data (Gold, 2012; Verlinden *et al.*, 2014). Imputations were performed separately for each study visit, with 5.3% or less of variables imputed per visit. Subsequently, IADL was calculated by summing the eight items.

Motor features

At baseline and follow-up visits, participants were screened for parkinsonian signs by research nurses using standardized methods. At baseline and repeatedly throughout the study period, these research nurses were trained by neurologists specialized in movement disorders to ensure consistent data on objective motor features. Importantly, these assessments were not used for diagnostic purposes, i.e. they were not considered in the process of establishing a diagnosis of parkinsonism.

We assessed the following motor features: any tremor, any hypo- and bradykinesia, rigidity, postural abnormalities, and postural balance. For features assessed on both sides, the highest score of both sides was used. Separate tremor observations (0 = absent, 1 = doubtful, 2 = present) on both sides included resting tremor, positional tremor, and intention tremor. We defined a composite tremor score ('any tremor') using the highest observation for any of the separate items on both sides. Of hypo- and bradykinesia observations, we assessed finger tapping on both sides and used the highest observation (0 = absent, 1 = doubtful, 2 = slowed down or reduced). In addition, we classified gait (0 = normal, 1 = shuffling and small steps, 2 = propulsion and festination), arm swing (0 = normal, 2 = reduced), and general impression of hypo- and bradykinesia (0 = absent, 1 = doubtful, 2 = present). A composite score for 'any hypo- or bradykinesia' was defined as the highest score for any separate hypo- or bradykinesia item. For rigidity, tone in both arms (0 = normal, 1 = elevated) was assessed. Postural balance was classified as 0 = normal, 1 = slightly disturbed or 2 = absent. Posture was classified as 0 = fitting age, 1 = head/neck/arms flexed or 2 = kyphosis and arms/legs flexed.

In addition, at each follow-up visit, subjects were asked whether they had fallen in the previous 12 months.

Non-motor features

We assessed cognitive functioning objectively using the MMSE (Folstein *et al.*, 1975), Stroop color word test (comprising three tasks; Stroop, 1935), Letter Digit Substitution Test (LDST; Smith, 1968), and Word Fluency Test (WFT; Welsh *et al.*, 1994). The abbreviated Stroop test consists of three

subtasks in which the participant is shown a (coloured) card with 40 items that have to be named (Stroop, 1935). In Trial 1, the participants are asked to name the printed words; in the second trial the participants are asked to name the printed colours; in the third trial the participants are asked to name the colour in which each colour-name is printed. For each trial, the time to complete the task was used as the outcome, which implies that a higher score indicates a worse performance. The LDST is a modified version of the Symbol Digit Modalities Test (Smith, 1968) and asks the participants to make as many letter-digit combinations as possible in 60 s, following an example that shows correct combinations. In the WFT, participants were asked to name as many animals as possible within 60 s (Welsh *et al.*, 1994). For both the WFT and LDST the number of correct answers was used as the outcome.

Subjective memory complaints were assessed using three questions, which could be answered by yes or no. These questions were: 'Do you have more trouble remembering things than before?'; 'Does it happen more often that you are on your way to do something and forget what you wanted to do?'; and 'Do you more often have trouble finding words during a conversation?'. Depressive symptoms were assessed during a home interview using the Dutch version of the original Centre for Epidemiological Studies Depression Scale (CES-D). The CES-D is a 20-item self-reported measure of symptoms, scored on a scale from 0 to 3 (Sawyer Radloff, 1977). Anxiety symptoms were assessed using the anxiety part of the Hamilton Anxiety and Depression Scale (Shiba *et al.*, 2000).

Blood pressure was measured by using a random-zero sphygmomanometer at the right brachial artery in sitting position after a 5-min rest. The average of two consecutive blood pressure measurements was used. By means of in-person interviews we obtained information on the use of blood pressure lowering medication (ATC codes C02, C03, C07, C08, and C09) as well as the use of laxative medication, which we used as a proxy for constipation as no data on stool frequency were available.

Statistical analysis

We used extended mixed models to investigate differences in trajectories of decline in daily functioning, motor features, and non-motor features, and with incident Parkinson's disease. In subanalyses, we explored which BADL component and IADL item was first to decline, and separately we used different thresholds for BADL and IADL scores to assess the proportion of prediagnostic cases and controls with any (score ≥ 1), moderate/severe (score ≥ 9), or severe (≥ 17) impairment.

Similar to a previous study (Verlinden *et al.*, 2016), we used a link function with quadratic splines to capture the distribution and account for ceiling effects of dependent variables with ceilings that were not dichotomous. To properly adhere to the distribution of dependent variables, we used the Bayesian information criterion (BIC) to estimate the optimal number and position of splines in a basic model including age, sex, their interactions with time, age \times time², time itself, time², and time³. For dichotomous or continuous dependent variables, a linear link function was used. Random intercepts and random slopes over time were included.

Time was calculated from clinical diagnosis of parkinsonism for Parkinson's disease cases, so that time = 0 corresponds to time of clinical diagnosis. For controls, we subtracted time to Parkinson's disease diagnosis of the matched Parkinson's disease case from the follow-up of the control so that at time = 0, follow-up time for controls equals that of their matched Parkinson's disease case.

We investigated up to cubic associations of incident Parkinson's disease with motor and non-motor features over time (i.e. interactions with time, time², and time³), adjusting for any non-time dependent effect of incident Parkinson's disease. For visualization of trajectories in motor and non-motor features, models including all interactions of Parkinson's disease up to time³ were used. All analyses were adjusted for the basic model of age, sex, education, their interactions with time, age \times time², time itself, time², and time³. Additionally, analyses on systolic and diastolic blood pressure were adjusted for use of blood pressure lowering drugs at the respective visits. We present trajectories of the last 14 years before (matched) diagnosis visually, since differences between patients with Parkinson's disease and control subjects generally occurred during that period.

As dementia before parkinsonism onset is no longer an exclusion criterion for Parkinson's disease in the MDS diagnostic criteria (Postuma *et al.*, 2015b) we explored how prediagnostic IADL, BADL, hypo- or bradykinesia and MMSE trajectories would be affected by the addition of parkinsonism patients with a preceding diagnosis of dementia (but without a clear secondary cause of parkinsonism) to the Parkinson's disease case group. In separate sensitivity analyses, we restricted trajectory analyses of IADL, BADL, hypo- or bradykinesia and MMSE to patients with Parkinson's disease who fulfilled a stricter case definition: their parkinsonism had to be diagnosed by a neurologist or geriatrician and they had to have had a positive response to dopaminergic medication.

We investigated rank ordering of motor features by subtracting the trajectories for these features of controls from the trajectories of Parkinson's disease cases and plotted these in the same figure. Hence, these trajectories reflect the additional decline in people that develop incident Parkinson's disease above decline in people not developing Parkinson's disease. After initial analyses showed that hypo- and bradykinetic features were highly frequent in prediagnostic Parkinson's disease patients, we also investigated rank ordering of these features separately. For non-motor features, instrument scales were highly discordant; therefore, we refrained from comparing rank ordering of these features.

As the spline link function estimates used to transform the dependent variables vary across analyses, effect sizes of associations cannot be readily interpreted. Hence, only significance of associations ($P < 0.05$) is reported. We used the 'WaldMult' function in R using nominal thresholds of statistical significance ($P < 0.05$) to determine when trajectories differed significantly between Parkinson's disease cases and controls. All analyses were performed using R version 3.1.2.

Results

The average (matched) age at clinical Parkinson's disease diagnosis was 78 years [standard deviation (SD) = 7 years]

and 56 Parkinson's disease cases (51%) were female. The mean Hoehn and Yahr score at time of clinical diagnosis was 1.6. Numbers of participants included per visit prior to Parkinson's disease diagnosis are presented in Table 2. As shown in Supplementary Table 2, selected controls had a slightly lower prevalence of hypo- and bradykinetic signs, tremor and postural imbalance than subjects who were not selected as controls.

Table 2 Number of incident Parkinson's disease cases and controls participating across visits

Visit	Time to Parkinson's disease, years (SD)	Cases, <i>n</i>	Controls, <i>n</i>
−4	−15.4 (2.4)	31	302
−3	−11.3 (2.8)	45	451
−2	−6.6 (2.3)	79	760
−1	−2.6 (1.8)	103	1004
1	1.5 (1.9)	70	944

Negative visits represent visits before Parkinson's disease diagnosis, while the positive visit represents the visit after diagnosis.

Daily functioning

Problems in IADL became more evident among Parkinson's disease cases than controls as early as 7.2 years before clinical diagnosis (Fig. 1A). This was followed by increasing difficulties in more physically driven BADL at 5.4 years (Fig. 1B). Of IADL domains, earliest differences were found for problems in travelling (7.7 years; Fig. 1C). Of BADL domains, problems in eating were earliest to differ between prediagnostic Parkinson's disease cases and controls (5.7 years; Fig. 1D).

An increasing proportion of prediagnostic Parkinson's disease patients had any IADL impairment or any BADL impairment in the last years before clinical diagnosis, but the incidence of any IADL impairment and BADL impairment also rose among controls, albeit to slightly lower levels (Supplementary Fig. 4A and B). When thresholds for impairment were increased, the relative difference between Parkinson's disease cases and controls became more evident for both BADL and IADL impairment, but the proportion of prediagnostic Parkinson's disease patients that was impaired also decreased for each (Supplementary Fig. 4C–F).

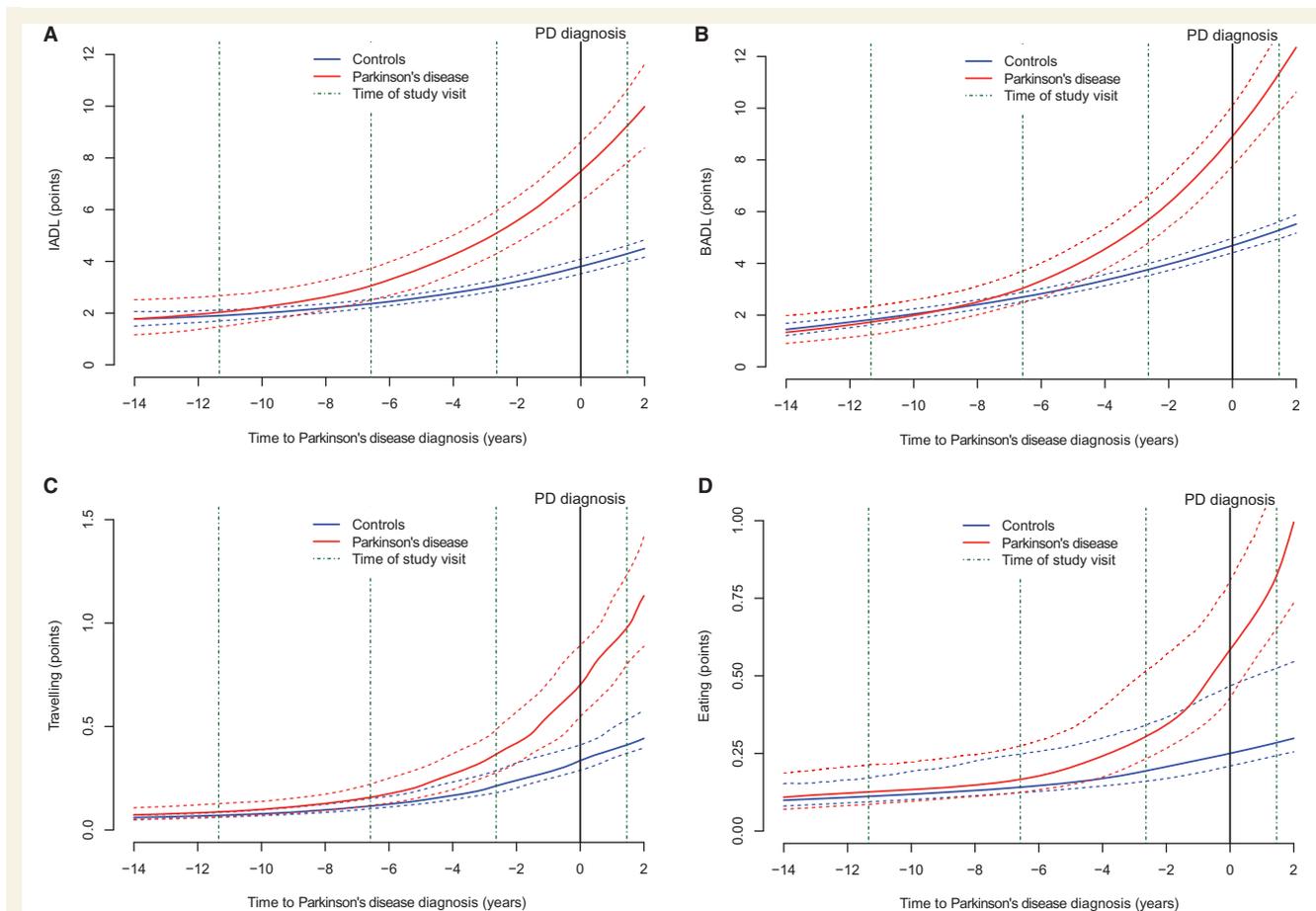


Figure 1 Trajectories of daily functioning. Y-axis denotes average score for Parkinson's disease patients and controls separately. (A) IADL; (B) BADL; (C) travelling; and (D) eating. Higher BADL and IADL scores correspond to higher impairment. For each group, correspondingly coloured dotted lines reflect confidence intervals. PD = Parkinson's disease.

Differences between Parkinson's disease cases and controls became statistically significant at the following time points: any IADL impairment –6.3 years, any BADL impairment –3.3 years, moderate or severe IADL impairment –5.6 years, moderate or severe BADL impairment –5.8 years, severe IADL impairment –3.7 years, severe BADL impairment –3.1 years.

Motor features

Parkinson's disease cases increasingly showed hypo- and bradykinetic signs throughout study follow-up, with a statistically significant overall difference compared to controls from 7.5 years before diagnosis onwards (Fig. 2A). Although tremor appeared to be more common in

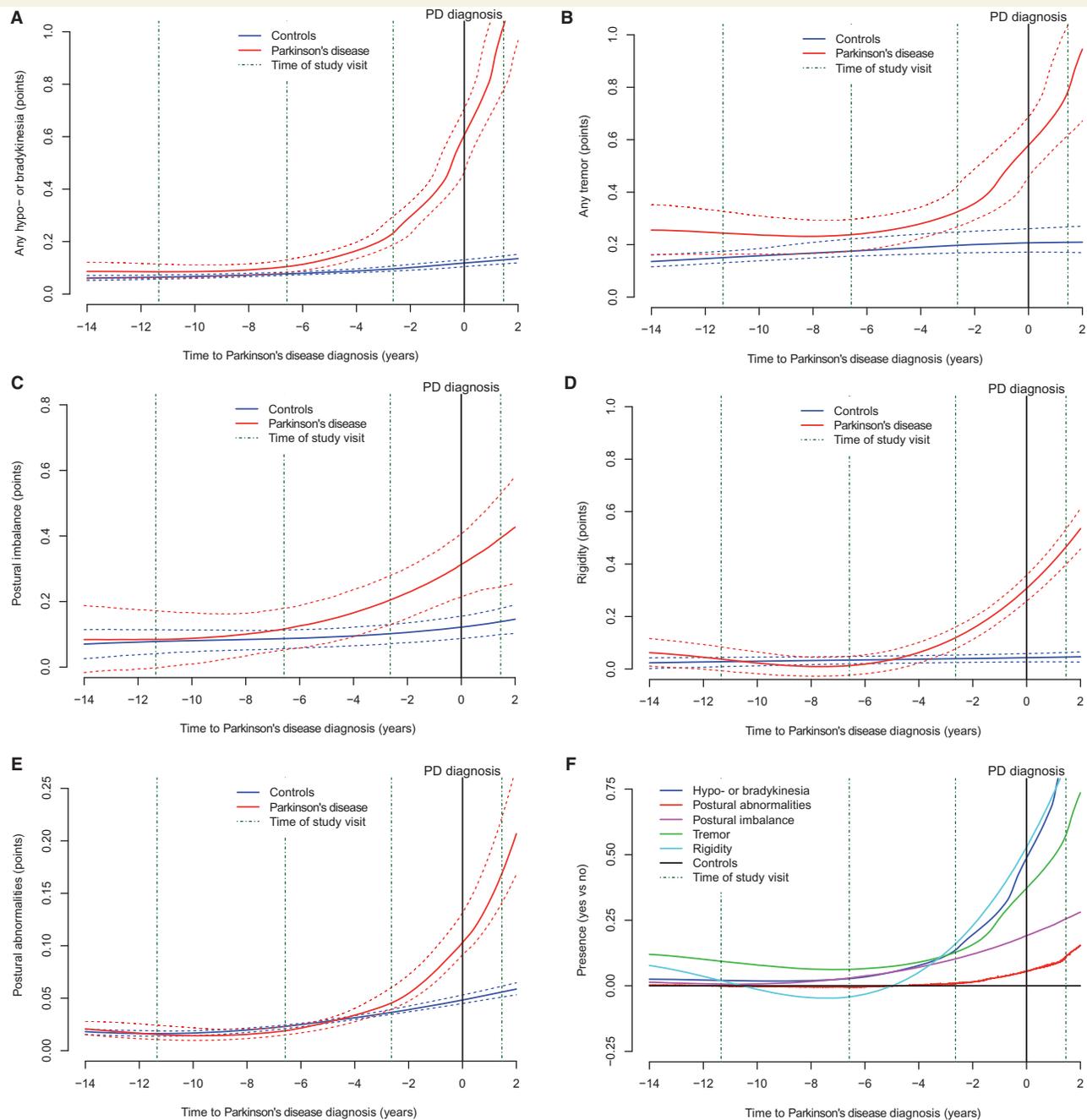


Figure 2 Trajectories of motor features. Trajectories of motor symptoms of Parkinson's disease cases and controls. Solid lines represent mean values and dotted lines the 95% confidence intervals. (A) Any hypo-/bradykinesia; (B) any tremor; (C) postural imbalance; (D) rigidity; and (E) postural abnormalities. (A–E) Average scores were calculated on a 0–2 scale, with 0 typically denoting normal, 1 doubtful, and 2 abnormal. PD = Parkinson's disease. (F) Trajectories of all motor symptoms in one graph. Trajectories are created by subtracting trajectories of controls from those of Parkinson's disease cases. Hence, $y = 0$ reflects the trajectory of controls. Of note, rigidity scores were doubled to facilitate comparison with the other motor features. For each group, correspondingly coloured dotted lines reflect confidence intervals.

Parkinson's disease cases as early as 14 years before Parkinson's disease diagnosis, differences with controls were only significant in the last 6.1 years (Fig. 2B). The presence of objective postural imbalance increased more rapidly in Parkinson's disease cases than in controls in the last 10 years before diagnosis, with significant differences in the last 3.8 years. (Fig. 2C). Around 3 years before Parkinson's disease diagnosis, the presence of rigidity and postural abnormalities became more frequent in Parkinson's disease cases than in controls (3.3 and 2.8 years, respectively; Fig. 2D and E). Parkinson's disease cases more frequently reported falling than controls as early as 14 years before diagnosis, but differences only became statistically significant 1.7 years before clinical diagnosis. At clinical diagnosis, rigidity, tremor and hypo- or bradykinesia were the most frequent features in Parkinson's disease cases (Fig. 2F).

Of hypo- and bradykinetic features, Parkinson's disease cases first more frequently had slowed finger tapping than controls throughout the entire pre-diagnostic phase, already from 15.8 years before clinical diagnosis onwards (Supplementary Fig. 1A). Parkinson's disease cases increasingly showed a reduced arm swing, with significant

differences in the last 8.6 years (Supplementary Fig. 1B). In the last 4 years, Parkinson's disease cases also more frequently presented a general impression of movement poverty or slowness (Supplementary Fig. 1C), and deteriorating gait followed in the last 4.5 years (Supplementary Fig. 1D). At clinical diagnosis, reduced arm swing and slowed finger tapping were the most common hypo- and bradykinetic feature among Parkinson's disease cases (Supplementary Fig. 1E).

Non-motor features

MMSE scores declined faster for Parkinson's disease cases than for controls throughout study follow-up, with significant differences around 5.6 years before diagnosis (Fig. 3A). On other cognitive tests, Parkinson's disease cases generally declined more rapidly than controls, and scores on the LDST were earliest to differ with significant worse scores for pre-diagnostic Parkinson's disease cases from 7.1 years before diagnosis onwards (Fig. 3B). Subsequently, Parkinson's disease cases had significantly worse scores on the Stroop tasks 3 (6.2 years; Fig. 3C), 1 (4.6 years) and 2 (3.8 years), and WFT (3.3 years; Fig. 3D).

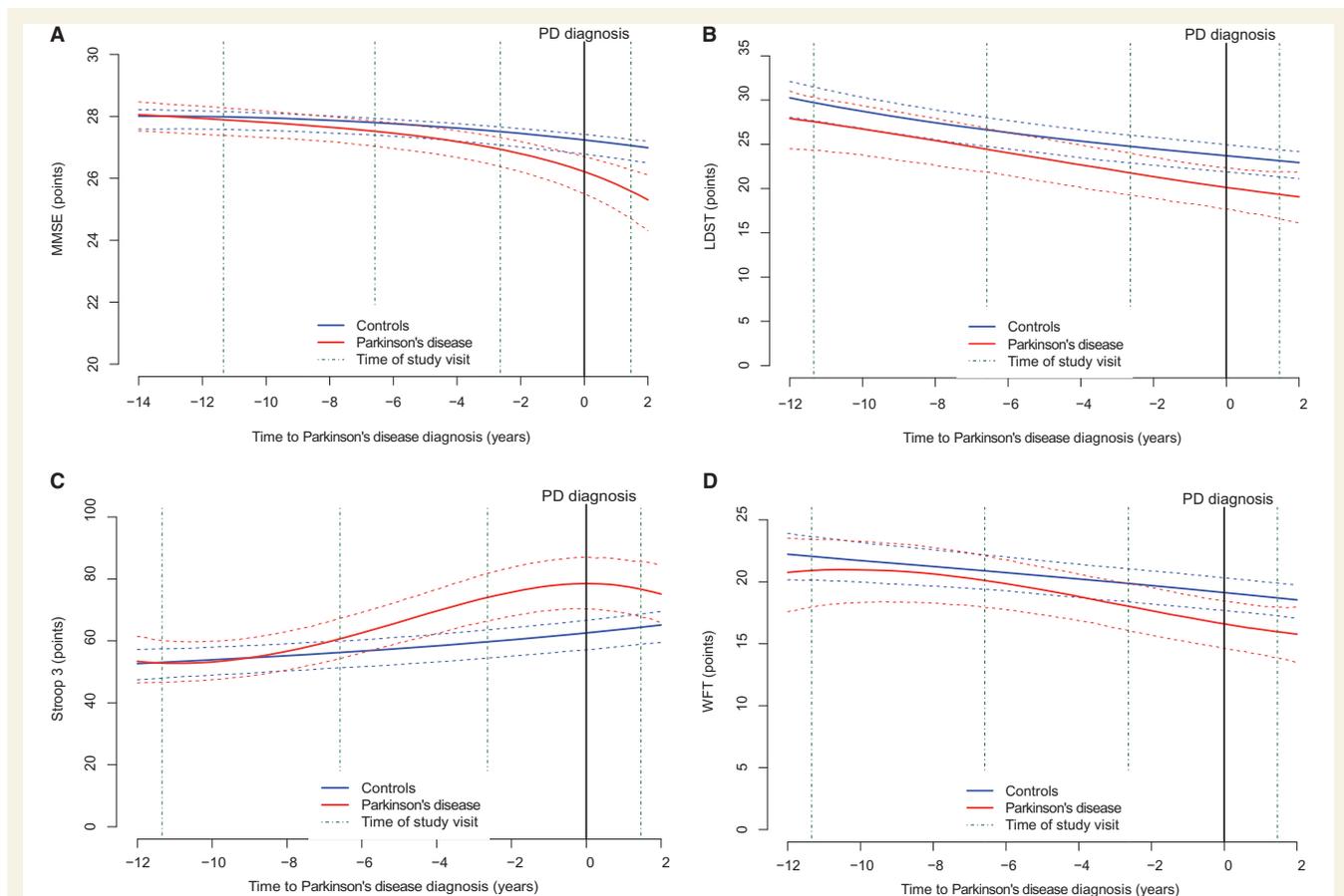


Figure 3 Trajectories of non-motor features. Y-axis denotes average score for Parkinson's disease patients and controls separately. (A) MMSE; (B) LDST; (C) Stroop test task 3; (D) WFT. For each group, correspondingly coloured dotted lines reflect confidence intervals. PD = Parkinson's disease.

Interestingly, Parkinson's disease cases did not more frequently report memory complaints until the last few years before diagnosis (1.5 years; Fig. 3B).

Although point estimates for anxiety scores were lower (i.e. worse) for Parkinson's disease cases as early as 16 years before clinical diagnosis, differences with controls only became significant in the final year before clinical diagnosis (Fig. 4A). Interestingly, depressive symptoms were transiently non-significantly more common between among Parkinson's disease cases ~15 years before Parkinson's disease diagnosis, and became significantly more common among Parkinson's disease cases in the last 2.3 years (Fig. 4B). Laxative medication was increasingly used by Parkinson's disease cases throughout study follow-up, and differences with controls became significant 2.4 years before diagnosis (Supplementary Fig. 4C). During the entire prediagnostic phase, there were no significant differences in systolic blood pressure between Parkinson's disease cases and controls, although systolic blood pressure appeared to rise less steeply over time and even declined somewhat around clinical diagnosis in Parkinson's disease

cases (Fig. 4D). Similarly, there were no significant differences in diastolic blood pressure between Parkinson's disease cases and controls, but the trajectory was less steep in Parkinson's disease cases.

Sensitivity analyses: trajectories of patients using alternative Parkinson's disease case definitions

During study follow-up, 43 subjects were first diagnosed with dementia and subsequently with parkinsonism during follow-up, and 30 of those did not have a clear secondary cause of parkinsonism. The mean interval between onset of dementia and onset of parkinsonism in these patients was 1.6 years. Combined prediagnostic trajectories of these patients together with patients who were already classified as Parkinson's disease cases in the main analyses are presented in Supplementary Fig. 2. Interestingly, differences between patients and controls in IADL (−7.1 years), BADL (−5.6 years) and hypo- or bradykinesia (−8.5 years) occurred at similar time points as in

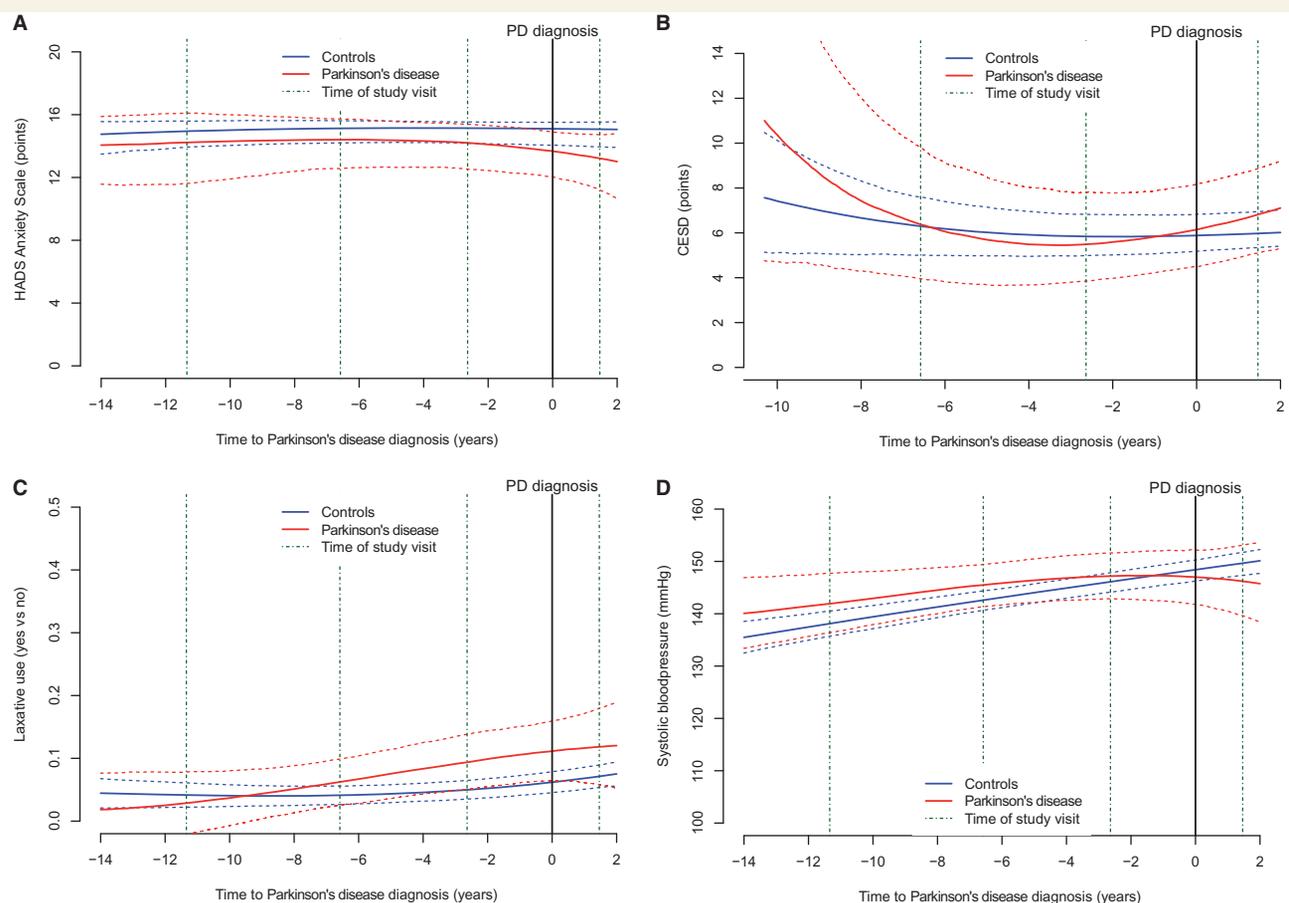


Figure 4 Trajectories of other non-motor features. Y-axis denotes average score for Parkinson's disease patients and controls separately. (A) Hamilton Anxiety and Depression Scale (HADS) anxiety subscale; (B) Center for Epidemiologic Studies Depression Scale (CES-D); (C) laxative use; (D) systolic blood pressure (importantly, these were seated blood pressure measurements only, not orthostatic blood pressure measurements). Of note, more anxiety corresponds to lower HADS scores. For each group, correspondingly coloured dotted lines reflect confidence intervals. PD = Parkinson's disease.

the main analyses, whereas the difference in MMSE scores occurred distinctly earlier (−9.1 years).

In separate sensitivity analyses, only 65 patients met a stricter case definition of Parkinson's disease. Their prediagnostic trajectories of IADL, BADL, hypo- or bradykinesia and MMSE were very similar to the original trajectories (Supplementary Fig. 3).

Discussion

In the years preceding clinical diagnosis, patients with Parkinson's disease increasingly experience problems in daily functioning and progressively show both motor and non-motor features. While movement poverty and tremor frequently appear as initial signs of Parkinson's disease, cognitive deficits are also common in early prediagnostic Parkinson's disease patients. These changes are initially reflected by impairments in complex tasks that require both motor and non-motor skills (IADL). The subsequent occurrence of additional features, including motor features such as rigidity, postural imbalance, and postural abnormalities, extends impairment to more physically oriented tasks (BADL).

Before further interpreting the results of this study, several limitations should be noted. First, the presence of motor features was assessed by research nurses, using subjective scores rather than dedicated quantification methods, and as research nurses were trained to classify signs of hypokinesia and signs of bradykinesia at the same time, we could not separately define bradykinesia from these assessments. However, these assessments were not considered for the diagnosis of parkinsonism, and as motor feature assessments were standardized and took place before participants were clinically diagnosed as Parkinson's disease cases or controls, the error that was introduced by their imprecise nature was probably the same in both groups. This suggests that true differences between groups may occur even earlier than we detected. Second, not all Parkinson's disease patients were examined in-person by movement disorder specialists and we lacked histologic confirmation on Parkinson's disease diagnosis, which probably introduced misclassification of Parkinson's disease cases. The detailed in-person and clinical information on the presence and possible causes of parkinsonism throughout the study period make it unlikely that we systematically misclassified one specific group of parkinsonism patients as Parkinson's disease patients (e.g. drug-induced parkinsonism). Third, we note that while we studied a wide range of features, our approach was not comprehensive; most noteworthy, we did not collect data on REM behaviour disorder (RBD) and olfactory function (Ross *et al.*, 2008; Postuma *et al.*, 2009). Fourth, we studied a population of subjects aged 55 years and older, and the average age of Parkinson's disease cases was somewhat higher than in general populations that also included younger persons. Therefore, our findings may not represent the prediagnostic phase of

young-onset Parkinson's disease. Finally, the number of Parkinson's disease cases for whom we had data on the very early prediagnostic phase (i.e. more than 10 years before diagnosis) was relatively low, so some caution is warranted for the interpretation of very early, statistically non-significant differences, most notably for tremor.

To date, two previous reports on long-term trajectories of features in prediagnostic Parkinson's disease patients have been published: a study in RBD patients, who are at extremely high-risk for Parkinson's disease and related α -synucleinopathies (Postuma *et al.*, 2012) and a registry-based study (Schrag *et al.*, 2015). Compared to those studies, our approach is novel for several reasons. First, we repeatedly and consistently assessed the presence of a wide range of motor and non-motor features over a time period of up to 23 years, and examinations were identical in subjects who were later diagnosed with Parkinson's disease and in those who were not. During the same period, we continuously followed all participants for the onset of clinical Parkinson's disease and applied consistent, standardized criteria for Parkinson's disease diagnosis. Second, study participants were included from the community irrespective of traits that strongly affect their risk of Parkinson's disease. This is a major difference with studies investigating high-risk populations such as RBD patients (Postuma *et al.*, 2015a) or *GBA*-mutation carriers (Beavan *et al.*, 2015), given that a substantial proportion of prediagnostic Parkinson's disease patients may not have these traits. Therefore, while such studies provide essential insight into prediagnostic changes in subgroups of patients with Parkinson's disease, community-based studies such as the Rotterdam Study harbour a sample of incident patients that is generally representative of the full spectrum of prediagnostic Parkinson's disease in the elderly population. Third, this study identified several novel prediagnostic changes in Parkinson's disease, including cognitive decline and deterioration in instrumental and basic daily functioning.

Importantly, we observed that patients with Parkinson's disease already started to decline in daily functioning years before clinical diagnosis. Impairment first became evident in tasks that require a combination of motor and cognitive skills, such as travelling, while problems in more physically oriented tasks increased as additional motor features appeared. Earliest deterioration in daily functioning was paralleled by an increase in movement poverty and slowness, which started to appear more frequently in patients with Parkinson's disease compared to control subjects 7 years before diagnosis. Of these, upper limb features such as reduced arm swing and slowed finger tapping preceded changes in gait. These results, as well as our observation that the presence of rigidity typically increased in the last few years before clinical diagnosis, correspond to findings from the RBD cohort (Postuma *et al.*, 2012). Furthermore, we observed that tremor presented as an early prediagnostic feature of Parkinson's disease (6 years before diagnosis) while postural imbalance increasingly occurred a few years

before clinical diagnosis, extending similar findings from the registry-based study (Schrag *et al.*, 2015). Of motor features, we further note that presence of postural abnormalities and falling increased sharply in the last years before diagnosis.

Strikingly, we also observed declining cognitive function scores in Parkinson's disease patients as early as 7 years before clinical diagnosis. Differences with age- and sex-matched controls were generally subtle; however, prediagnostic Parkinson's disease patients in particular declined earlier in processing speed and executive function, whereas memory decline started later. This is in line with the previous observation that cognitive impairment can be quite advanced in clinical Parkinson's disease patients with relatively high MMSE scores (Burdick *et al.*, 2014). Of note, in our study, the follow-up for LDST, Stroop test and WFT was shorter than for MMSE, which may have prevented us from detecting statistically significant differences between patients with Parkinson's disease and control subjects at an even earlier moment for these tests. Furthermore, the tests that we used relatively under-represented specific cognitive dysfunction of Parkinson's disease, such as attentional-executive dysfunction and impaired visuoperceptual skills. Specific tests designed for cognitive function in Parkinson's disease patients may have detected differences between patients with Parkinson's disease and controls at an even earlier moment, possibly also showing greater amplitude of differences.

Interestingly, we observed that as impairments in daily functioning rose, prediagnostic Parkinson's disease patients increasingly reported anxiety symptoms. Similarly, Parkinson's disease patients increasingly reported depressive symptoms, but differences with controls only became significant around diagnosis. Of other non-motor features, laxative use among Parkinson's disease patients increased years before clinical diagnosis, which is similar to findings on constipation from another population-based study (Abbott *et al.*, 2001). However, differences between patients with Parkinson's disease and controls were only significant for a small part of the prediagnostic period. This may be caused by our analysis method of treating laxative use as a proxy for constipation, which probably led to an underestimate of its true prevalence. Furthermore, in contrast to previous studies which identified hypotension as a risk factor for Parkinson's disease (Noyce *et al.*, 2012), we did not observe lower blood pressures for Parkinson's disease patients across prediagnostic trajectories. Importantly, these were sitting blood pressure measurements only, not orthostatic blood pressure measurements. Repeated measures on orthostatic hypotension may be more sensitive to detect early autonomic function deterioration in prediagnostic Parkinson's disease patients.

Decline in daily functioning is increasingly recognized as an important determinant of quality of life in patients with Parkinson's disease (Simpson *et al.*, 2014) and several trials have shown that self-perceived performance in daily activities by Parkinson's disease patients can be improved by non-invasive interventions (Tomlinson *et al.*, 2012;

Sturkenboom *et al.*, 2014). At the same time, symptomatic treatment modalities for various motor and non-motor features of early clinical Parkinson's disease are advancing (Castrìo *et al.*, 2014; Connolly and Lang, 2014; Goetz and Pal, 2014). Our observation that decline in daily functioning starts years before clinical parkinsonism may open the door to even earlier symptomatic intervention trials (i.e. in prodromal Parkinson's disease patients), and our data on the occurrence of prediagnostic features (most notably: objective cognitive decline) may aid in the identification of subjects who would benefit most from such early symptomatic treatment. However, we note that while our approach (nested case-control analyses using repeated assessments in a general population) is very powerful to detect early differences between prediagnostic Parkinson's disease patients and controls, the relative risk estimates presented graphically cannot be directly interpreted as prospective predictive estimates for incident Parkinson's disease, such as the risk estimates in the recent MDS criteria for prodromal Parkinson's disease (Berg *et al.*, 2015). In a previous study, we investigated whether a single, rapid assessment of non-motor features, both separately and combined, could identify subjects at high risk of Parkinson's disease (Darweesh *et al.*, 2016b). That method is less powerful than the method used here, but given its simple and rapid nature probably more closely mirrors potential future population-wide screening for Parkinson's disease. Therefore, while we believe that assessments of IADL, BADL and objective cognitive functioning may be useful additions to the MDS criteria for prodromal Parkinson's disease, their prospective predictive value is still to be formally examined.

Furthermore, while our observation of autonomic and limbic features in prediagnostic Parkinson's disease is in line with Braak's theory (Braak *et al.*, 2003) our observation of movement poverty and slowness as well as cognitive decline years before clinical diagnosis are not. Taken together, these findings support the notion that pathological processes of Parkinson's disease may already be too advanced in newly diagnosed patients for putative protective interventions to have substantial effects (Lang *et al.*, 2013). Data from this study may provide context for selection of subjects for neuroprotective trials that target Parkinson's disease patients before a clinical parkinsonism diagnosis is possible.

In conclusion, prediagnostic Parkinson's disease patients often first experience problems in instrumental daily activities, in parallel with the occurrence of early motor and cognitive deficits. Once additional prediagnostic features arise, decline in daily functioning accelerates and extends to problems in more physically oriented tasks.

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Supplementary material

Supplementary material is available at *Brain* online.

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