Prediagnostic presentations of Parkinson's disease in primary care: a case-control study

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Summary

Background Parkinson's disease has an insidious onset and is diagnosed when typical motor features occur. Several motor and non-motor features can occur before diagnosis, early in the disease process. We aimed to assess the association between first presentation of several prediagnostic features in primary care and a subsequent diagnosis of Parkinson's disease, and to chart the timeline of these first presentations before diagnosis.

Methods We identified individuals with a first diagnosis of Parkinson's disease and those without Parkinson's disease from Jan 1, 1996, to Dec 31, 2012, from The Health Improvement Network UK primary care database. Codes were extracted for a range of possible prediagnostic or early symptoms, comprising motor features (tremor, rigidity, balance impairments, neck pain or stiffness, and shoulder pain or stiffness), autonomic features (constipation, hypotension, erectile dysfunction, urinary dysfunction, and dizziness), neuropsychiatric disturbances (memory problems, late-onset anxiety or depression, cognitive decline, and apathy), and additional features (fatigue, insomnia, anosmia, hypersalivation and rapid-eye-movement sleep behaviour disorder) in the years before diagnosis. We report the incidence of symptoms recorded in more than 1% of cases per 1000 person-years and incidence risk ratios (RRs) for individuals with and without Parkinson's disease at 2, 5, and 10 years before diagnosis.

Findings 8166 individuals with and 46 755 individuals without Parkinson's disease were included in the study. Apathy, REM sleep behaviour disorder, anosmia, hypersalivation, and cognitive decline were all reported in less than 1% of people per 1000 person-years and were excluded from further analyses. At 2 years before Parkinson's disease diagnosis, the incidence of all studied prediagnostic features except neck pain or stiffness was higher in patients who went on to develop Parkinson's disease (n=7232) than in controls (n=40 541). At 5 years before diagnosis, compared with controls (n=25 544), patients who went on to develop Parkinson's disease (n=4769) had a higher incidence of tremor (RR 13·70, 95% CI 7·82–24·31), balance impairments (2·19, 1·09–4·16), constipation (2·24, 2·04–2·46), hypotension (3·23, 1·85–5·52), erectile dysfunction (1·30, 1·11–1·51), urinary dysfunction (1·96, 1·34–2·80), dizziness (1·99, 1·67–2·37), fatigue (1·56, 1·27–1·91), depression (1·76, 1·41–2·17), and anxiety (1·41, 1·09–1·79). At 10 years before diagnosis of Parkinson's disease, the incidence of tremor (RR 7·59, 95% CI 1·11–44·83) and constipation (2·01, 1·62–2·49) was higher in those who went on to develop Parkinson's disease (n=1680) than in controls (n=8305).

Interpretation A range of prediagnostic features can be detected several years before diagnosis of Parkinson's disease in primary care. These data can be incorporated into ongoing efforts to identify individuals at the earliest stages of the disease for inclusion in future trials and to help understand progression in the earliest phase of Parkinson's disease.

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See Comment page 27

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Introduction

Parkinson's disease is the second most common neurodegenerative disease worldwide and incidence is rising with changing population demographics.[1] Present treatment strategies are aimed at improving symptoms, but increasing efforts are being made to trial neuroprotective drugs that potentially slow or prevent the development of symptoms.[2] These drugs are most likely to be beneficial when used early in the disease process, before substantial neuronal loss has occurred.[2,3] Diagnosis of Parkinson's disease relies on the identification of the classical motor symptoms, which are incorporated into clinical diagnostic criteria.[4] However, at least 50% of the nigrostriatal neurons have already been lost at the time of diagnosis and pathological abnormalities are thought to start in other brain regions earlier than nigrostriatal degeneration.[5] Compared with people who do not develop Parkinson's disease, several non-motor symptoms occur more frequently in patients with Parkinson's disease before the onset of typical motor symptoms, including depression, constipation, anosmia, and fatigue.[6] When in the disease course each of these symptoms first occurs and whether they could be detected in primary care is unknown.[7] Insight into the first clinical presentations of these prediagnostic features would help to delineate the pathophysiology of early Parkinson's disease progression and to identify people at increased risk of development of overt Parkinson's

disease, who would be eligible for inclusion in clinical trials of neuroprotective strategies.

We used a large primary care database in the UK with prospectively recorded data on presentations, diagnoses, and prescriptions to assess the association between several prediagnostic features and a subsequent diagnosis of Parkinson's disease, and to chart the timeline of these presentations before diagnosis.

Methods

Study design and data sources

See Online for appendix

For **THIN** see http://www.thin-uk.com

After a comprehensive meta-analysis on possible prediagnostic features of Parkinson's disease,[8] we undertook a study in The Health Improvement Network (THIN) to compare prediagnostic features that were recorded in primary care in individuals who developed Parkinson's disease with those in matched controls. THIN holds anonymised longitudinal medical records for over 11 million individuals registered with more than 500 general practices in the UK, representing around 6% of the population.[9] These data are collected from general practices that have elected to join the THIN quality data recording scheme using the Vision practice management software (In Practice Systems, London, UK). THIN is a large and comprehensive source of patient data from consultation records. Information on symptoms, diagnoses, interventions, and referrals to secondary care are electronically recorded as Read codes, a hierarchical coding system used in UK primary care.[10,11] Information recorded in the system includes data on all drug prescriptions and records of health indicators such as height, weight, blood pressure, smoking status, and laboratory test results recorded by general practitioners (GPs), and information on levels of social deprivation (Townsend score) as quintile scores from 1 (least deprived) to 5 (most deprived). THIN data are representative of the UK general practice population in terms of demographics and frequency and type of consultations requested by patients, and electronically coded diagnoses have been shown to be accurate when compared with the gold standard (GP questionnaire, primary care medical record, or hospital correspondence).[12,13] Data on smoking levels in THIN are similar to those reported in The Health Survey for England.[14]

Only pseudonymous patient data are collected in THIN. No patient names, addresses, dates of birth, or National Health Service (NHS) numbers are available; therefore, explicit patient consent is not necessary. Patients are informed of the use of their data via posters and general practice leaflets, and they have the option to opt out of the data collection. The THIN data collection scheme has been approved by an NHS multicentre research ethics committee and has been reviewed several times since data collection started. Additionally, strict governance rules exist concerning the use of THIN, and stringent legal and technical restrictions are in place to protect patient confidentiality. The University College London Scientific Review Committee approved the present study.

Study population

We identified all individuals in THIN who had a Read code diagnosis of Parkinson's disease and at least two anti-parkinsonian drug prescriptions. A similar method for identification of people with Parkinson's disease has been validated in another large primary care database in the UK.[15] Diagnostic Read codes for Parkinson's disease were identified using published methods (appendix).[16] The earliest date of Read code diagnosis or anti-parkinsonian drug prescription was taken as the index date. Individuals with diagnoses before age 50 years were excluded, as were those with secondary parkinsonism, dementia before Parkinson's disease diagnosis, drug-induced parkinsonism, or schizophrenia, because these individuals are likely to have had substantial exposure to dopamine antagonist drugs.

We used stratified sampling within each GP practice to extract a control population without a diagnosis of Parkinson's disease but similar characteristics in terms of age, sex, and registration period. Within each GP practice, we divided patients with Parkinson's disease into categories according to sex, 5-year age band, and year of index date (ie, diagnosis). Up to six controls per Parkinson's disease patient were selected in the same sex, age band, and registration period categories by a random sampling routine in Stata. For individuals without Parkinson's disease, age and registration period were defined using the date of a GP consultation selected using the random sampling routine in Stata (index date).

We included data recorded from Jan 1, 1995, or when practices were consistently contributing good levels of data, defined as using acceptable mortality recording[17] and acceptable computer usage in terms of the numbers of consultations, health measurements, and prescriptions.[18] Individuals were included only if they had at least 1 year of such data before the index date. This inclusion criterion also ensured that individuals had at least 1 year between registration with the GP practice and diagnosis of Parkinson's disease, which limits the possibility of inclusion of patients with Parkinson's disease that was diagnosed previously but first recorded by the new GP during the patient registration period.[19] Thus, patients with Parkinson's disease included in the analyses were those diagnosed between Jan 1, 1996 (after exclusion of individuals with less than 1 year of follow-up from Jan 1, 1995) and Dec 31, 2012 (the most recent full year of data available at the time of analysis).

Data extraction

We examined symptoms previously reported to be associated with subsequent diagnosis of Parkinson's disease on the basis of published work, which are also likely to be recorded in the patients' electronic health record. On the basis of a recently undertaken systematic

literature review[8] and a further Medline search for the terms "pre-diagnostic" OR "prediagnostic" OR "prodromal" and "Parkinson's disease" from March, 2011, to April, 2014, symptoms initially included in the analysis were late-onset (>50 years of age) anxiety and depression, fatigue, apathy, insomnia, rapid eye movement (REM) sleep behaviour disorder, balance impairments, dizziness, hypotension, anosmia, hypersalivation, constipation, urinary dysfunction, erectile dysfunction, memory problems, neck pain or stiffness, shoulder pain or stiffness, rigidity, tremor, and cognitive decline. All symptoms were defined using Read code lists (appendix).[16] Additionally, we used prescriptions for anxiolytics, antidepressants, drugs for constipation, hypnotics, and drugs for erectile dysfunction to identify symptoms of anxiety, depression, constipation, insomnia, and erectile dysfunction, respectively. A symptom presentation was identified if either the Read code or prescription of a symptom-specific drug was recorded. Any symptoms or diagnoses coded shortly after registration with the GP potentially represent prevalent health issues and not new diagnoses (ie, prevalent cases). Therefore, using a previously described method,[19] we plotted the monthly incidence of each prediagnostic symptom within 2 years after GP registration and the point at which the incidence became roughly constant was selected to define a period within which diagnoses were excluded. By this method, the exclusion period was 1 year after GP registration for anxiety or depression and 6 months for all other symptoms (data not shown).

Statistical analysis

We calculated the incidence and 95% CIs of prediagnostic symptom presentations per 1000 person-years for each year within 10 years before the index date for individuals with and without Parkinson's disease. We excluded symptoms with a recorded prevalence of less than 1% in patients with Parkinson's disease in THIN from further analysis. We calculated the risk ratios (RRs) and 95% CIs for prediagnostic symptom presentations at 2, 5, and 10 years before index dates (Parkinson's disease diagnosis or a date selected using the random sampling routine in Stata for those without a diagnosis of Parkinson's disease).

For the periods from 0–2 years, 2–5 years, and 5–10 years before to the index date, we present the overall occurrence of prediagnostic symptoms as absolute numbers and percentages.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. All authors had full access to all the data in the study and the corresponding author had final responsibility for the decision to submit for publication.

Results

8166 individuals with any follow-up data and 46755 without Parkinson's disease were included in the study. At 2 years, 7232 patients were included in the Parkinson's disease group and 40541 in the control group; at 5 years these numbers were 4769 and 25544, and at 10 years they

	Total		With ≥2 years of retrospective data		With ≥5 years of retrospective data		With ≥10 years of retrospective data	
	Parkinson's disease (n=8166)	Controls (n=46755)	Parkinson's disease (n=7232)	Controls (n=40541)	Parkinson's disease (n=4769)	Controls (n=25544)	Parkinson's disease (n=1680)	Controls (n=8305)
Sex								
Men	4859 (60%)	27684 (59%)	4323 (60%)	24076 (59%)	2885 (60%)	15330 (60%)	1024 (61%)	5017 (60%)
Women	3307 (40%)	19071 (41%)	2909 (40%)	16465 (41%)	1884 (40%)	10214 (40%)	656 (39%)	3288 (40%)
Age at index date	75 (68–81)	74 (68–80)	75 (68–80)	74 (68–80)	75 (68–81)	75 (68–80)	75 (68–80)	75 (68–80)
Person-years of data available before index date	5 (3–5)	5 (3–5)	5 (4–5)	5 (4–5)	9 (7–11)	9 (7–11)	12 (11–14)	12 (11–14)
Smoking status								
Never	4396 (54%)	20589 (44%)	3892 (54%)	17938 (44%)	2609 (55%)	11386 (45%)	913 (54%)	3723 (45%)
Past	2076 (25%)	12196 (26%)	1880 (26%)	10763 (27%)	1376 (29%)	7556 (30%)	590 (35%)	2892 (35%)
Present	711 (9%)	7594 (16%)	622 (9%)	6556 (16%)	393 (8%)	4059 (16%)	122 (7%)	1202 (15%)
Data missing	983 (12%)	6376 (14%)	838 (12%)	5284 (13%)	391 (8%)	2543 (10%)	55 (3%)	488 (6%)
Social deprivation (Townsend score)								
1 (least deprived)	2397 (29%)	12572 (27%)	2178 (30%)	11091 (27%)	1524 (32%)	7344 (29%)	559 (33%)	2557 (31%)
2	1948 (24%)	11086 (24%)	1718 (24%)	9675 (24%)	1147 (24%)	6165 (24%)	405 (24%)	2031 (24%)
3	1572 (19%)	9318 (20%)	1385 (19%)	8069 (20%)	857 (18%)	5015 (20%)	304 (18%)	1628 (20%)
4	1268 (16%)	7862 (17%)	1108 (15%)	6731 (17%)	716 (15%)	4096 (16%)	242 (14%)	1242 (15%)
5 (most deprived)	756 (9%)	4800 (10%)	654 (9%)	4079 (10%)	415 (9%)	2439 (10%)	145 (9%)	733 (9%)
Data missing	225 (3%)	1117 (2%)	189 (3%)	896 (2%)	110 (2%)	485 (2%)	25 (1%)	114 (1%)

Data are number (%) or median (IQR).

Table 1: **Characteristics of patients with Parkinson's disease and controls**

	Within 0 to <2 years		≥2 years to <5 years		≥5 years to <10 years	
	Parkinson's disease (n=7232)	Controls (n=40 541)	Parkinson's disease (n=4769)	Controls (n=25 544)	Parkinson's disease (n=1680)	Controls (n=8305)
Tremor	2946 (41%)	184 (<1%)	311 (7%)	118 (<1%)	29 (2%)	41 (<1%)
Constipation	2326 (32%)	7598 (19%)	1196 (25%)	3890 (15%)	335 (20%)	1202 (14%)
Fatigue	761 (11%)	2129 (5%)	430 (9%)	1472 (6%)	180 (11%)	618 (7%)
Dizziness	725 (10%)	2411 (6%)	486 (10%)	1629 (6%)	206 (12%)	723 (9%)
Depression	696 (10%)	1724 (4%)	312 (7%)	1035 (4%)	94 (6%)	409 (5%)
Shoulder pain or stiffness	528 (7%)	2263 (6%)	407 (9%)	1729 (7%)	175 (10%)	803 (10%)
Anxiety	624 (9%)	1505 (4%)	333 (7%)	1039 (4%)	136 (8%)	504 (6%)
Neck pain or stiffness	301 (4%)	1613 (4%)	224 (5%)	1301 (5%)	128 (8%)	667 (8%)
Urinary dysfunction	338 (5%)	815 (2%)	167 (4%)	459 (2%)	53 (3%)	170 (2%)
Erectile dysfunction	293/4323 (7%)	1434/24 076 (6%)	242/2885 (8%)	1072/15 330 (7%)	116/1024 (11%)	416/5017 (8%)
Insomnia	314 (4%)	1286 (3%)	190 (4%)	850 (3%)	85 (5%)	386 (5%)
Balance impairments	300 (4%)	379 (1%)	78 (2%)	196 (1%)	21 (1%)	62 (1%)
Hypotension	153 (2%)	346 (1%)	80 (2%)	204 (1%)	27 (2%)	61 (1%)
Memory problems	197 (3%)	520 (1%)	61 (1%)	187 (1%)	8 (<1%)	47 (1%)
Rigidity	201 (3%)	52 (<1%)	11 (<1%)	36 (<1%)	3 (<1%)	16 (<1%)

Data are number of patients (%). Symptoms listed according to frequency in the 0–2 year column. Only individuals who had follow-up for the complete time period were included (ie, at least 2, 5, and 10 years, respectively).

Table 2: **Number of patients with symptoms before diagnosis or index date**

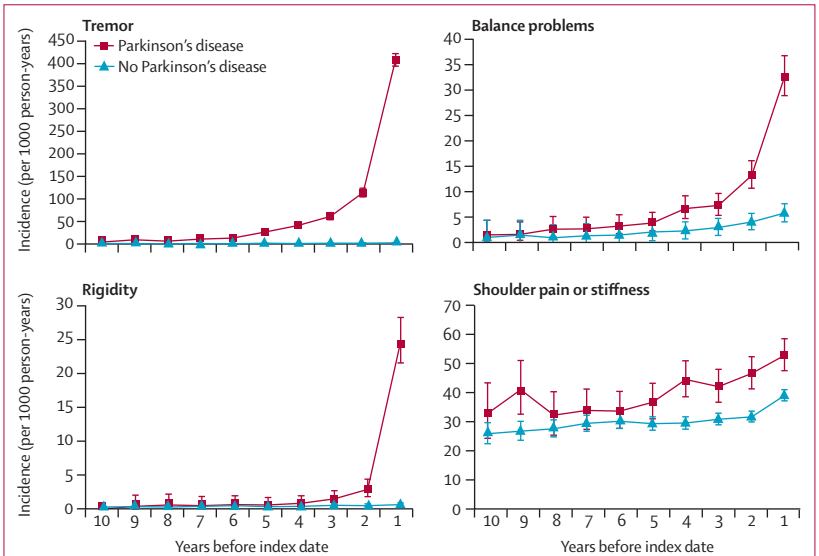

Figure 1: **Incidence of motor symptoms of Parkinson's disease**
Bars are 95% CIs, based on the sample size of each group. Neck pain and stiffness symptoms are not shown because the difference between groups was not significant at any year.

were 1680 and 8305. The characteristics between the two groups were similar with the exception of smoking status, for which the number of present smokers in the Parkinson's disease group was about half that in the control group, and social deprivation was lower in the Parkinson's disease group than in controls (table 1).

Prevalence of REM sleep behaviour disorder, apathy, cognitive decline, anosmia, and excessive saliva were less than 1% and were therefore excluded from further analyses. The most common prediagnostic symptom of Parkinson's disease within 2 years before diagnosis was tremor, with 41% of individuals reporting symptoms to their GP compared with less than 1% of controls (table 2).

Most presentations of tremor occurred within 2 years before the Parkinson's disease diagnosis (RR 32·54, 95% CI 24·94–42·90), although incidence of tremor was already higher in the Parkinson's disease compared with the control group at 5 years (13·70, 7·82–24·31) and 10 years (7·59, 1·11–44·83) before diagnosis (figure 1; table 3). For the other motor features, the group of individuals later diagnosed with Parkinson's disease had a higher incidence of balance impairments at 2 years and 5 years before diagnosis, shoulder pain or stiffness at 2 years, and rigidity at 2 years compared with controls (figure 1; table 3). Incidence of neck pain or stiffness did not differ between the groups (table 3).

Within the 2 years before Parkinson's disease diagnosis, the most common neuropsychiatric presentation was depression, which occurred in 10% of individuals with later diagnosis of Parkinson's disease and 4% of controls (table 2). Incidence of depression with onset over the age of 50 years was higher in patients with Parkinson's disease than in those without at 2 years (RR 2·15, 95% CI 1·85–2·49) and at 5 years (1·76, 1·41–2·17), but not at 10 years (2·00, 0·19–12·21) before diagnosis of Parkinson's disease (figure 2; table 3). For the other neuropsychiatric features, compared with controls the individuals later diagnosed with Parkinson's disease had a higher incidence of prediagnostic anxiety with onset over the age of 50 years at 2 years and at 5 years and memory problems at 2 years (figure 2; table 3).

Constipation was the most common autonomic complaint within the 2 years before Parkinson's disease diagnosis, with 32% of patients in the Parkinson's disease group affected versus 19% of controls (table 2). Incidence of constipation was higher in those with Parkinson's disease than in those without at 10 years (RR 2·01, 95% CI 1·62–2·49), 5 years (2·24, 2·04–2·46), and 2 years before diagnosis (2·44, 2·29–2·59; figure 3; table 2). Dizziness was first reported in 10% of patients with Parkinson's disease and 6% of controls within 5 years of diagnosis and at 2 years, and hypotension was noted in 2% compared with 1% of patients at 5 years and at 2 years (figure 3; table 3). Erectile dysfunction was more common in those who went on to develop Parkinson's disease compared with controls at 5 years and 2 years before diagnosis, and urinary dysfunction occurred more frequently at 5 years and 2 years before diagnosis (figure 3; table 3).

Individuals later diagnosed with Parkinson's disease also had a higher incidence than controls of insomnia (RR 1·38, 95% CI 1·11–1·70; figure 2; table 3) and of fatigue (1·79, 1·55–2·06) at 2 years before diagnosis, and of fatigue at 5 years before diagnosis (1·56, 1·27–1·91; figure 3; table 3).

	At 2 years	At 5 years	At 10 years
Tremor	32·54 (24·94–42·90)	13·70 (7·82–24·31)	7·59 (1·11–44·83)
Constipation	2·44 (2·29–2·59)	2·24 (2·04–2·46)	2·01 (1·62–2·49)
Fatigue	1·79 (1·55–2·06)	1·56 (1·27–1·91)	1·52 (0·96–2·32)
Dizziness	1·80 (1·58–2·05)	1·99 (1·67–2·37)	1·30 (0·85–1·92)
Depression	2·15 (1·85–2·49)	1·76 (1·41–2·17)	2·00 (0·19–12·21)
Shoulder pain or stiffness	1·35 (1·17–1·56)	1·11 (0·91–1·35)	1·24 (0·85–1·79)
Anxiety	1·89 (1·58–2·25)	1·41 (1·09–1·79)	1·39 (0·86–2·16)
Neck pain or stiffness	1·01 (0·83–1·23)	1·18 (0·94–1·47)	0·98 (0·65–1·42)
Urinary dysfunction	2·27 (1·80–2·85)	1·96 (1·34–2·80)	1·92 (0·84–4·06)
Erectile dysfunction	1·30 (1·06–1·57)	1·30 (1·11–1·51)	1·00 (0·56–1·69)
Insomnia	1·38 (1·11–1·70)	1·18 (0·86–1·58)	1·46 (0·82–2·48)
Balance impairments	2·43 (1·69–3·44)	2·19 (1·09–4·16)	0·67 (0·02–5·00)
Hypotension	3·03 (2·18–4·18)	3·23 (1·85–5·52)	1·37 (0·25–5·08)
Memory problems	2·13 (1·44–3·11)	0·87 (0·26–2·24)	3·46 (0·29–30·20)
Rigidity	2·63 (1·11–5·79)	1·39 (0·25–5·15)	..*

Symptoms listed according to frequency in the at 2 years column. Data are incidence risk ratios (95% CI) for patients with Parkinson's disease compared with controls. *Cannot be calculated because an insufficient number of presentations was recorded.

Table 3: **Incidence risk ratios of symptom presentations recorded in over 1% of patients at 2, 5, and 10 years before diagnosis**

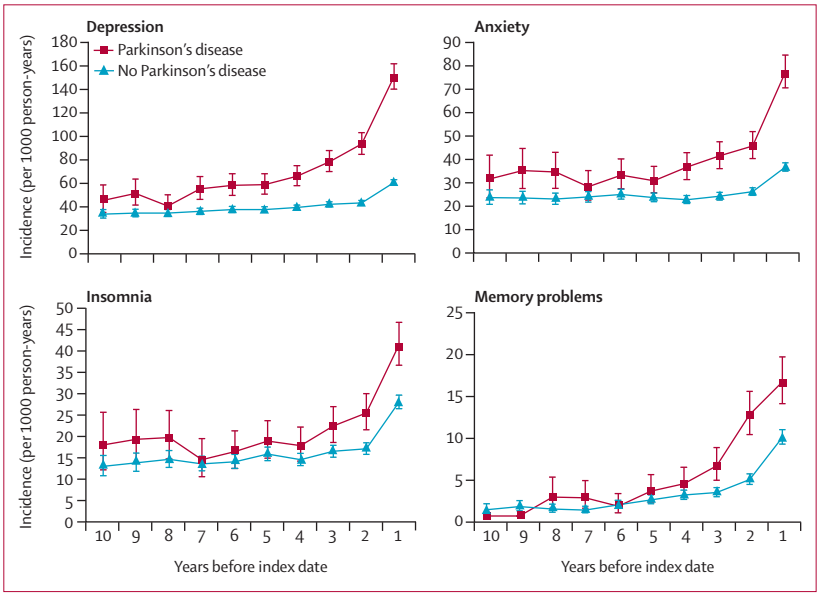

Figure 2: **Incidence of neuropsychiatric symptoms and insomnia**
Bars are 95% CIs, based on the sample size of each group.

Discussion

In this study, we show that individuals with a subsequent diagnosis of Parkinson's disease present to their primary care physicians with several motor and non-motor features of Parkinson's disease that might represent prediagnostic features. At 2 years before Parkinson's disease diagnosis, except neck pain or stiffness, the incidence of all examined features with prevalence of 1% or more was higher in patients who went on to develop Parkinson's disease than in controls. At 5 years before diagnosis, compared with controls, patients with Parkinson's disease had a higher incidence of tremor, balance impairments, constipation, hypotension, erectile dysfunction, urinary dysfunction, dizziness, fatigue, depression, and anxiety. At 10 years before diagnosis of Parkinson's disease, the incidence of tremor and constipation was already higher in those who went on to develop Parkinson's disease than in controls.

Some non-motor symptoms have previously been shown to occur frequently before diagnosis of Parkinson's disease compared with controls,[8] but several of the symptoms investigated in this Article, such as fatigue, dizziness, hypotension, and memory problems, have not been reported quantitatively before. Many of the previously identified prediagnostic features of Parkinson's disease are non-specific, such as anosmia or constipation, whereas others are specific but rare, such as REM sleep behaviour disorder. Several ongoing or recently completed studies[20–22] aim to address more than one of these features, together with other markers such as genetic risk factors or investigations such as transcranial sonography or ^{123}I-2β-carbomethoxy-3β-(4-iodophenyl)-N-(3-fluoropropyl)-nortropane (^{123}I-β-CIT SPECT), to harness their combined potential to identify the earliest stages of Parkinson's disease and define at-risk populations.[23] However, to the best of our knowledge, only one study[24] has addressed a combination of postulated premotor symptoms together in a primary care population (panel). That nested case-control study, which was based on a smaller database of about 12 000 patients, addressed a range of features in the period within 2 years before Parkinson's disease diagnosis, and found that patients

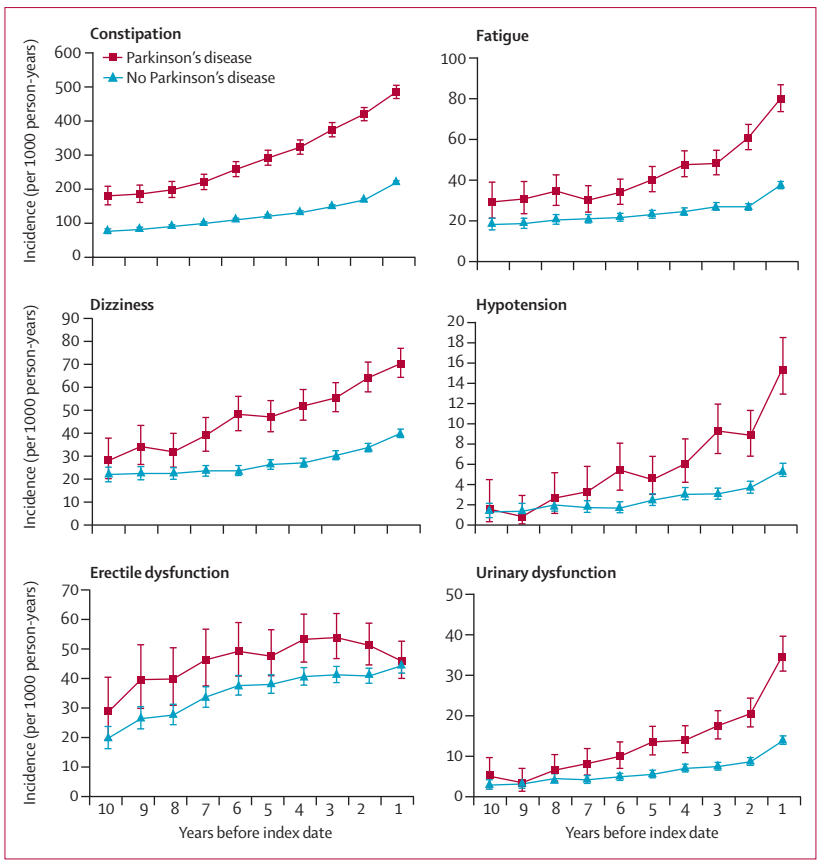

Figure 3: **Incidence of autonomic symptoms and fatigue**
Bars are 95% CIs, based on the sample size of each group.

with Parkinson's disease more often presented with functional somatic symptoms, constipation, hyperhidrosis, and sleep disorders than did controls. In another study,[25] 93 patients with Parkinson's disease who were retrospectively asked about prediagnositic symptoms reported a mean of 7·6 symptoms before diagnosis.

The present study is, to our knowledge, the largest and most comprehensive of its kind, in which a large number of prediagnostic features were investigated in the same cohort. Additionally, to our knowledge, this study is the first to chart the first occurrence of these early symptom presentations over time before diagnosis of Parkinson's disease. The results of this study support the existence of a long prediagnostic phase of Parkinson's disease, which comprises both motor and non-motor features.[6,26,27] These features include some of the typical symptoms of Parkinson's disease, such as tremor, rigidity, or balance impairments, which can be too non-specific, atypical or difficult to interpret in isolation to be used for diagnosis of Parkinson's disease at initial presentation. Also, even if symptoms are typical there can be a delay between their first presentation and diagnosis of Parkinson's disease. The high incidence of tremor, even 10 years before diagnosis of Parkinson's disease, might be due to some patients already having clinical features of mild but typical Parkinson's disease before formal diagnosis. In addition, an association between essential tremor and Parkinson's disease has been suggested,[28] which suggests that some patients might have had essential tremor before developing Parkinson's disease or that they had a long duration of isolated tremor as a feature of their Parkinson's disease. However, the data in this analysis do not allow differentiation of these syndromes.

The features that we identified as occurring many years before diagnosis included those that are often regarded as symptoms of advanced Parkinson's disease (eg, hypotension, balance impairments, and urinary dysfunction), that are non-specific (eg, fatigue, insomnia, and constipation), or that they are likely to be initially diagnosed as different disorders (eg, depression and anxiety, memory problems, or shoulder pain). Nevertheless, all of these symptoms are not only common in typical Parkinson's disease,[29] but also might represent the earliest stages of Parkinson's disease.

We noted a temporal pattern of different prediagnostic features that supports the present hypothesis of pathophysiological progression of Parkinson's disease,[5,30] first involving autonomic, limbic, and somatomotor systems, followed by the midbrain and substantia nigra. The similar incidence of neck pain or stiffness in individuals with subsequent Parkinson's disease and controls might be either because neck pain is a less specific symptom or because it is not a prediagnostic feature of Parkinson's disease.

The incidence of presentation of autonomic dysfunction in primary care was increased in people who went on to develop Parkinson's disease compared with controls. In particular, constipation was more common in patients than in controls already 10 years before diagnosis. Constipation is thought to be an early feature of Parkinson's disease,[31–34] and peripheral Parkinson's disease pathology, including α-synuclein neuropathology in the enteric nervous system, might precede the classic changes in midbrain and limbic areas.[7] Other autonomic features with which individuals presented to their primary care physicians were dizziness, urinary dysfunction, hypotension, and erectile dysfunction (in men), which are rarely reported prediagnostic features of Parkinson's disease.[7,31,35] Erectile dysfunction has been associated with a diagnosis of Parkinson's disease more than 10 years later.[36] In our study, its incidence was higher in patients than in controls already 5 years before diagnosis of Parkinson's disease. However, its incidence seemed to be similar to that in controls at the time of Parkinson's disease diagnosis, possibly because erectile dysfunction is under-reported in the Parkinson's disease group at the time of diagnosis of Parkinson's disease or patients did not complain about this symptom in the face of other, more troublesome symptoms.

Neuropsychiatric presentations, such as depression and anxiety with first onset over the age of 50 years and memory problems, were also more common in patients than controls in the years before diagnosis of Parkinson's disease, supporting the early occurrence of these non-motor complications.[7] Memory problems were more frequently reported by patients than controls 2 years before diagnosis, and this finding might be an underestimate because cognitive impairment might be under-reported or under-recognised and because dementia was an exclusion criterion for this study.

Recognition of this prediagnostic phase of Parkinson's disease is helpful in understanding its pathophysiological progression and for the development of strategies to identify individuals at risk in the general population. Our finding of multiple prediagnostic symptoms, and their pattern of presentation in the 10 years before diagnosis, suggests that screening might be feasible in the general population; screening for these symptoms is possible with established instruments,[37] but would need to be carefully considered and several preconditions, such as benefit of early treatment, should be fulfilled for such a future screening programme.[38]

Furthermore, this study provides clinical support for the early involvement of extrastriatal structures in the development of Parkinson's disease, as suggested by findings from pathological and imaging studies in Parkinson's disease and incidental Lewy body disease.[35] Parkinson's disease has been suggested to begin in extranigral structures, including the olfactory bulb or lower brainstem nuclei, or even sympathetic nervous system structures such as the gastric myenteric plexus.[5] Early non-motor symptoms, such as autonomic dysfunction, and memory problems and psychiatric impairment, including symptoms often thought to be non-specific, such as fatigue and insomnia, occurred more frequently in individuals with later diagnosis of Parkinson's disease than in controls in this study, and might be a result of this early brainstem or extranigral pathological change.

The main limitation of this study is that data were not collected through active enquiry about prediagnostic features of Parkinson's disease, but were derived from already collected longitudinal primary care data. Thus, we cannot be certain about the diagnostic accuracy of the symptom presentations. Some overestimation might have occurred—eg, for balance impairments, which are usually thought of as a feature of advanced Parkinson's disease rather than early Parkinson's disease. The incidence of some factors was probably underestimated, especially for those that are not particularly troublesome or are under-recognised, such as anosmia, hypersalivation, apathy, or REM sleep behaviour disorder. This underestimation might explain the low incidence of these specific symptoms in primary care data and might have led to underestimation of other symptoms. Nevertheless, the sample size in this study was large; therefore, the data are probably a good representation of presentation of Parkinson's disease in primary care in the UK. Additionally, the data were collected prospectively without a recall or selection bias towards diagnosis of Parkinson's disease and therefore are a true-life representation of presentations to primary care. The results therefore provide information on the type of data that could be used in future studies in routine clinical settings in primary care.

Our approach has other limitations. Co-occurrence of symptoms in the same person might provide further important information on risk of Parkinson's disease; however, our analysis included only first presentation of each symptom in isolation, irrespective of other already existing symptoms, and does not allow conclusions regarding the predictive value of combinations of symptoms for Parkinson's disease within one person. Assessment of risk associated with co-occurring symptoms is an important area for future study.

Patients and controls were overall well matched, although the patients had lower social deprivation. Thus, a bias due to lower social deprivation cannot be excluded. However, the absence of a difference between groups in neck pain or stiffness argues against this. Also, such a bias would not explain the increase in incidence of symptoms in the years approaching diagnosis of Parkinson's disease.

A further limitation of the study is that the diagnosis of Parkinson's disease in primary care is likely to be delayed. This is a limitation particularly for the 2 year timepoint, when many patients are likely to already have had mild parkinsonism. Conversely, occurrence of symptoms associated with reduced survival might have been underestimated, especially for the 10 year timepoint. This underestimation might apply particularly to the autonomic features that were identified in the shorter time periods before diagnosis. Furthermore, the decreasing number of patients with longer follow-up precluded examination of first occurrence more than 10 years before diagnosis. Thus, presentations at an even earlier stage were probably

***Panel:* Research in context**

Systematic review

We searched Medline up to Sept 4, 2014, for reports in English with the terms "Parkinson's disease" and "case-control" and "prodromal" or "prediagnostic" or "pre-diagnostic", yielding 42 reports. We repeated the search replacing "case-control" with "cohort", yielding 33 articles. We screened these reports for content and identified only one paper[24] that addressed a wide range of prediagnostic symptoms of Parkinson's diseases in a case-control or cohort study design.

Interpretation

In this large study of a representative primary care population, we show for the first time the increased incidence of a wide range of motor and non-motor presentations within 10 years before diagnosis of Parkinson's disease. These manifestations of Parkinson's disease can be troubling enough to lead to clinical presentation in routine primary care consultations before a clinical diagnosis, and provide insight into the pathophysiological process in the earliest stages of Parkinson's disease.

missed and the first onset of some of the prediagnostic features occurs probably even earlier.

Finally, the diagnosis of Parkinson's disease might not have been confirmed by specialist input in all cases and a few patients probably had an atypical parkinsonian syndrome, which might have become apparent during later follow-up.[39] Also, the data are not representative for young-onset Parkinson's disease because patients under age 50 years were excluded, but this population represents only a small proportion of individuals with Parkinson's disease.

Contributors

AS conceived and designed the study and wrote the first draft. LH did the analysis. All authors contributed to the design and interpretation of the results.

Declaration of interests

We declare no competing interests.

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