Identification of prodromal presentations of Parkinson's disease in a large German healthcare database

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Abstract

Background: Parkinson's disease is typically diagnosed when the characteristic motor features of bradykinesia, rigidity or tremor occur. However, a number of studies have documented the motor and non-motor features of the disease in the prodromal phase, often several years before diagnosis. Large routine care databases offer the possibility to identify clinical features that predate the diagnosis. It is currently unclear whether recordings of diagnoses in routine care in Germany can identify these clinical features in a primary care setting.

Methods: We used a large routine database containing data from primary care consultations in the German healthcare system to examine presentations predating the diagnosis of Parkinson's disease. This retrospective case-control study was based on data from the Disease Analyzer database (IQVIA) and included 17,702 patients with Parkinson's disease and 17,702 non-PD controls matched for age, sex, and index year. We analyzed the prevalence of 15 defined diagnoses and symptoms documented within 2 years, ≥2 to <5, and ≥5 to <10 years prior to the index date in patients with and without PD. Logistic regression analyses were conducted to assess the association between PD and the predefined diagnoses.

Results: The prevalence of motor, neuropsychiatric and autonomic features was higher in those with a later diagnosis of Parkinson's disease than controls for all three periods except for rigidity in the ≥2 to <5 and ≥5 to <10-year periods and erectile dysfunction in the most recent period before diagnosis. The clinical presentation recorded in the greatest percentage of patients was depression, followed by dizziness, insomnia, and constipation, but these were also common in the control population. The odds ratios were highest for increase in tremor (OR 6.42 (5.61–7.35)) followed by balance impairment and memory problems, particularly in the latest period before diagnosis, and by constipation particularly in the earliest period examined.

Conclusion: The prodromal features of Parkinson's disease could be identified in this large primary care database in Germany with similar results to those found in previous database studies despite differences in methodologies and systems. The presence of these clinical features may aid primary care practitioners by supporting the early diagnosis of Parkinson's disease in clinical practice and clinical management.

Background:

Parkinson's disease is the second most common neurodegenerative disease in the world after Alzheimer's disease, with the number of patients affected in Germany estimated at 420,371 in 2015 (Heinzel et al. 2018). Patients with Parkinson's disease are primarily treated in an outpatient setting by primary care physicians in collaboration with specialists (Heinzel 2018; Nerius et al. 2017), with additional inpatient care as necessary (Nerius et al. 2017; 2020, Rosqvist et al. 2021). The disease results in a considerable burden for patients and carers (e.g., Kalmpokini et al. 2020) as well as insurance and social costs (Bovolenta et al. 2017; Hjalte et al. 2021). Similarly to dementia, diagnosing the disease early is important in order to improve care (Noyce AJ et al. 2017; Rees et al. 2019; Postuma et al. 2019; Dommershuizen et al. 2021) or even intervene preventatively (Smedinga et al. 2020; Chen et al. 2021). As a result, early and prodromal symptoms have been the focus of considerable research over the last 20 years (Gonera et al. 1997; Rees et al. 2019; Poortvliet et al. 2020; Berg D et al. 2021). Whilst this research focused primarily on allowing inclusion of prodromal symptoms into research studies, the recognition of prodromal clinical features that are recognized in routine clinical practice also offers the opportunity to inform clinical recognition in routine care. Other than qualitative studies on attitudes amongst primary care physicians (Plouvier et al. 2014) few studies have examined this topic in primary care settings. Following a number of smaller studies (Gonera et al. 1997), a large primary care study in the UK examined prodromal features in 7,232 patients with Parkinson's disease and 40,541 controls (Schrag et al. 2015). In a series of simultaneous case control studies involving the same patients, they demonstrated that a range of previously reported prodromal features can be identified in primary care and

often occur many years before the eventual diagnosis. However, these results have not yet been replicated in other large datasets, and it is unclear whether these clinical features are also identified in other healthcare settings. Furthermore, while the UK study examined the initial occurrence of prodromal symptoms, longer-standing symptoms with onset >10 years before diagnosis of PD may have been missed. In the present study, we used a large German database with data from a number of German primary care practices to examine this issue.

Methods:

Database

Data from the Disease Analyzer database (IQVIA) in Germany were used for this study. This database has been described extensively in the literature (Rathmann et al. 2018). Briefly, it contains demographic, diagnosis, and prescription data obtained in anonymized format from general and specialized practices in Germany. Diagnoses are coded using the German adaptation of the International Classification of Diseases, 10th revision (ICD-10), and prescriptions are coded using the Anatomical Classification of Pharmaceutical Products of the European Pharmaceutical Marketing Research Association (EphMRA). Several variables (e.g., age of physician, specialty, community size category, and German federal state) were used for the selection of the panel of practices for this analysis. Approximately 3% of German general and specialized practices are included in the Disease Analyzer database – 1,164 general practices in total. Previous research has shown that this database is representative of primary care practices in Germany (Rathmann et al. 2018). The database has previously been used for epidemiological studies in the field of Parkinson's disease (Reese et al. 2015; Warda et al., 2019).

Study population

We identified all patients aged ≥18 years who received a first diagnosis of Parkinson's disease (ICD-10 G20, G21) between January 2000 and December 2019 (index date). Patients had to be registered for at least twelve months prior to the index date to be included, so as to avoid including patients with existing diagnoses of Parkinson's disease. Individuals without PD were matched (1:1) to those with PD by sex, age, and index year. In patients without PD, the index date corresponded to a randomly selected visit date between January 2000 and December 2019.

Study outcomes

We recorded the occurrence of defined diagnoses and symptoms previously reported to be associated with later diagnosis of Parkinson's disease prior to the index date in patients with and without PD. Three periods were analyzed: Within 0 to <2 years, ≥2 years to <5 years, and ≥5 years to <10 years prior to the index date.

The diagnoses analyzed included:

Motor features: tremor (ICD-10: R25.1), shoulder pain or stiffness (ICD-10: M25.5), neck pain or stiffness (ICD-10: M54.2), rigidity (ICD-10: M24.5, M24.6, M25.6), balance impairments (ICD-10: R26),

Neuropsychiatric symptoms: depression (ICD-10: F32, F33), anxiety (ICD-10: F41), memory problems (ICD-10: F06.7, R41), insomnia (ICD-10: G47.0, G47.9),

Autonomic function disturbances: constipation (ICD-10: K59.0), urinary dysfunction (ICD-10: N39.3, N39.4, N39.9), erectile dysfunction (ICD-10: F52), hypotension (ICD-10: I95), dizziness (ICD-10: R42); and fatigue (ICD-10: F32, G93.3, R53).

Statistical analyses

Baseline characteristics (age and sex) were compared between patients with PD and patients without PD using McNemar tests for sex and Wilcoxon signed-rank tests for age. Logistic regression analyses were conducted to assess the association between PD and the predefined diagnoses/symptoms. To reduce the risk of error due to multiple comparisons, p-values lower than 0.01 were considered statistically significant. Finally, analyses were conducted using SAS 9.4 (SAS institute, Cary USA).

Results:

Our study included 17,702 patients with Parkinson's disease and 17,702 controls. Of these, 14,986 with Parkinson's disease und 15,708 without had been followed at least 2 years before the index date, 10,378 with and 12,335 without Parkinson's disease had at least 5 years of follow-up, and 5,591 with and 6,440 without Parkinson's disease had at least 10 years of follow-up data prior to the index date. The groups did not differ with regard to sex and age (see Table 1).

Motor features

Tremor was the most common motor diagnosis in the period up to 2 years before diagnosis of Parkinson's disease (11% in the Parkinson's disease vs 2% in the control group). The greatest increase in the number of patients recorded as experiencing tremor occurred within 2 years of diagnosis of Parkinson's disease (OR 6.42; 95%CI 5.61–7.35), with an OR of 3.42 (95%CI 2.77–2.78) in the period of 2–5 years before diagnosis and an OR of 2.44 (95%CI 1.98–3.02) 5–10 years before diagnosis (see Table 3 and Figure 1). Similar results were found for balance problems and shoulder

pain/stiffness and neck pain/stiffness in all three periods, but ORs were smaller for shoulder pain/stiffness and neck pain/stiffness (see Fig 1). Rigidity was less common overall, and there was no difference between the Parkinson's disease group and the control group except in the period up to 2 years before the index date (see Table 3).

Neuropsychiatric symptoms

Depression was the most common diagnosis in the 2 years before the index date (25%) and was recorded more often in the Parkinson's disease group than in the control group in all three periods (see Table 2), with ORs of 2.56 (2.40–2.73) in 2 years or less, OR 2.41 (2.23–2.61) in 5–10 years before the index date, and OR 2.12 (1.91–2.36) in the period ≥10 years before the index date (see Table 3 and Fig 2). Despite lower prevalence rates, the occurrence of anxiety, insomnia, fatigue, and memory problems was similarly higher in Parkinson's disease patients than in controls in all three periods before the index date.

Autonomic function disturbances

Constipation was the most common autonomic function disturbance in the period up to 2 years before diagnosis, affecting 12% of those with Parkinson's disease. It was at least twice as common in those with Parkinson's disease than in controls in all three periods (see Tables 2 and 3 and Fig 3). Similarly, confusion, hypotension, and urinary disturbances were more common in those with later diagnosis of PD than in controls in all three periods. Amongst the diagnoses and symptoms examined, the only symptom for which there were no differences between those later diagnosed with Parkinson's disease and controls was erectile dysfunction.

Discussion

In this study, based on data from a large database of diagnoses in the German healthcare system, we found an increased prevalence of a number of ICD-10 diagnoses previously associated with the prodromal phase of Parkinson's disease in patients later diagnosed with Parkinson's disease (Noyce et al. 2016; Rees et al. 2019). This is in keeping with previous studies using similar databases in other healthcare systems, which reported that clinical features of the prodromal phase of Parkinson's disease can be detected in routinely collected diagnostic data in primary and secondary care settings (Schrag et al. 2015). In contrast to a previous study in the UK, we examined prevalent diagnoses and recorded symptoms that were present in the years preceding the diagnosis, independently of their first occurrence. This allows for greater detection of features of prodromal Parkinson's disease that arise long before the onset of the classic motor features that lead to a diagnosis of Parkinson's disease. Given that the prodromal phase can potentially be decades long, this may be more reflective of prodromal features with a very early onset. The results were comparable with those of earlier studies with a higher prevalence of motor, autonomic, and neuropsychiatric features as well as sleep behavior disorder and fatigue in patients up to 10 years before diagnosis than in matched controls. The first study examining the prodromal phase of Parkinson's disease in a large primary care dataset in the UK study was able to show, based on a systematic review (Noyce et al. 2012), that features of prodromal Parkinson's disease could be detected not only in the context of specific studies but also in primary care settings many years before the diagnosis of Parkinson's disease. We were able to confirm these findings for all clinical features examined in a database pertaining to the German healthcare system. The studies differed in terms of the type of setting, data collection, and coding (e.g., using ICD-10 codes rather than Read codes in the present study), as well as study methodology,

such as examination of the prevalence rather than the incidence of prodromal features and use of logistic regression analyses rather than Cox regression analyses. Despite these methodological differences between the studies, however, the similarity of the respective findings supports the robustness of the results and demonstrates that, regardless of differences in healthcare settings, coding systems, and precise methodologies, prodromal features of Parkinson's disease can be detected years before eventual diagnosis.

Other studies in medical registers have produced similar results, and prognostic models based on these studies have been proposed (Schrag et al. 2019; Searles-Nielsen et al. 2017). Schrag et al. proposed a model using the features identified in the UK primary care study which had a diagnostic accuracy with an area under the curve of 0.80 (Schrag et al. 2019). Searles-Nielsen et al. proposed a prognostic model comprising 536 diagnostic parameters und procedure codes to predict the diagnosis of Parkinson's disease more effectively than a simpler model comprising only demographics, constipation, anosmia, and REM-sleep behavior disorder (Searles-Nielsen et al. 2017). These models are likely to improve and continuously incorporate additional features that are being identified. Between 2008 and 2018 the number of potential markers for prediagnostic Parkinson's disease has more than doubled, with the number of studies in this area increasing and the Movement Disorders Society updating its prodromal Parkinson's disease criteria (Postuma and Berg 2019). These additional features were not examined in the current study.

In the following, we discuss the applicability of our findings to clinical practice for each of the three diagnostic areas. In order to prompt interventions in primary care, findings must be sufficiently common (see Bohlken et al. 2017; Bohlken et al. 2021), whereas rarer features are important for the development of novel research and theories.

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Motor features

Non-specific tremor (ICD-10: R25.1) and changes in gait and mobility (ICD-10: R26) were increased in all three periods in patients with Parkinson's disease with substantially higher odds ratios compared to controls. Although the OR decreased as the time before diagnosis increased, they were already increased more than 5 years before the formal diagnosis of Parkinson's disease. This has also been found consistently in other studies (e.g., Schrag et al. 2015; Faust et al. 2020; Yuan et al. 2021). While both presentations are included in the core features of Parkinson's disease (Armstrong et al. 2020), primary care physicians may not make a formal diagnosis until there is greater clinical certainty (Eichler et al. 2015). This is reflected in the higher ORs closer to time of diagnosis (Yuan et al. 2021). Similarly, although the relatively non-specific symptoms of shoulder pain/stiffness and neck pain/stiffness were reported more commonly in patients later diagnosed with PD than in controls many years before diagnosis, the ORs were relatively small, indicating a lower diagnostic value. On the other hand, we did not find an increased report of rigidity as an early feature predating diagnosis in the earlier periods, although this symptom was also increased in the period immediately preceding the diagnosis. These results suggest that, amongst the motor features, tremor and balance problems have the greatest clinical diagnostic value on a population basis.

Neuropsychiatric symptoms

While neuropsychiatric symptoms are not ranked among the cardinal manifestations of Parkinson's disease (Postuma et al. 2015), mainly due to their common occurrence in the general population, they are among the most common non-motor features of

Parkinson's disease, especially in the advanced stages. We found that depression, anxiety, memory problems, and insomnia were all recorded more commonly in patients later diagnosed with Parkinson's disease than in controls in all periods, including 5–10 years before diagnosis, with two- to three-fold increased risk of Parkinson's disease. This further emphasizes the importance of neuropsychiatric features as early prodromal features that should alert the clinician to the possibility of an underlying diagnosis of Parkinson's disease, particularly when they first emerge in later life (Kazmi et al. 2020). As these clinical presentations are relatively common, this has implications for a wider population of patients. Further investigation or elicitation of specific characteristics, e.g., REM-sleep behavior disorder or hallucinations, or identification of other prodromal features may be helpful in identifying those at particularly increased risk.

Autonomic function disturbances

The most common autonomic function disorders were dizziness and constipation, with a more than two-fold increase across all three periods. While the ORs were highest closest to diagnosis for most diagnoses examined, for constipation it was highest in the earliest period, where the prevalence was more than three times higher. This is in keeping with the hypothesis of early involvement of the gastrointestinal system in the pathogenesis of Parkinson's disease. Urinary disturbances, dizziness, and hypotension and fatigue were also increased in all three time periods but with a lower overall prevalence. On the other hand, erectile dysfunction appeared less strongly associated with Parkinson's disease diagnosis in the period just preceding the diagnosis, which is similar to previous findings (Schrag et al. 2015). However, the prevalence rates of recorded diagnoses were low, making these findings less robust. Autonomic features have not traditionally been considered features of prodromal or

even early Parkinson's disease. However, this study and other analyses of primary care databases suggest that, whilst some symptoms such as dizziness and constipation are relatively common in the general population, they may also reflect underlying early Parkinson's disease. A number of studies have reported that almost half of the patients with Parkinson's disease reported constipation in the prediagnostic phase (Gan et al. 2018; Schrag (Zhelev) et al. 2019). As for neuropsychiatric presentations, there may be specific features such as postural hypotension or associated findings such as slowness or memory problems or, in selected cases, examinations that can help identify those at risk of Parkinson's disease.

For the practicing clinician, increased alertness with regard to the diagnosis of Parkinson's disease in individuals exhibiting any of the clinical features associated with PD, use of a specific algorithm, such as that used by (Schrag, (Anastahsiu, Ambler) et al. 2019), may help estimate an individual's risk of developing the disease in primary care.

Limitations

This study's main strength is its very large sample size and the representativeness of the database, allowing for the detection of prodromal features on a population basis. It is the first study addressing this issue in the German healthcare system and includes data from more than 17,000 patients with Parkinson's disease, exceeding the number of cases of the original UK study, which covered over 8,000 patients. Prospective cohort studies for research purposes typically have much smaller sample sizes (e.g., Mahlknecht et al. 2015; Gaenslen et al. 2014; Noyce et al. 2017). On the other hand, these studies can provide further detail and improved diagnostic accuracy, which

studies using routinely collected data cannot provide (see Lit.). Furthermore, the diagnosis made and recorded in primary care practices is typically delayed and specific studies in specialist settings will likely provide an earlier and more accurate diagnosis (Breen et al. 2013). We also did not attempt to combine different clinical features and therefore did not examine the value of combined features or clusters. Finally, only a selected number of prodromal features were examined and others were not included, particularly more recently recognized or rarer features or those not typically presenting in primary care, such as REM-sleep behavior disorder or anosmia (Högl et al. 2018).

Conclusion

Diagnoses associated with prodromal features of Parkinson's disease can already be identified several years before the diagnosis of Parkinson's disease in practices in the German healthcare system. These prodromal presentations can not only help us to understand the progression of the disease but may also support early diagnosis. The results of our analysis confirm the findings of the early study based on the UK healthcare system, using a slightly different analytical methodology and focusing on the occurrence of new and already existing (prevalent) diagnoses rather than new (incident) presentations, thus capturing symptoms that may have started much earlier. Particularly in combination with the exploration of specific features and with investigations, understanding the prevalence of these symptoms and the strength of their association with Parkinson's disease can lead to early diagnosis of Parkinson's disease and more appropriate treatment.

References

Armstrong MJ, Okun MS. Diagnosis and treatment of Parkinson disease: a review. JAMA. (2020) 323:548–60. 10.1001/jama.2019.22360 - DOI - PubMed

Berg D, Borghammer P, Fereshtehnejad SM, Heinzel S, Horsager J, Schaeffer E, Postuma RB. Prodromal Parkinson disease subtypes - key to understanding heterogeneity. Nat Rev Neurol. 2021 Jun;17(6):349-361. doi: 10.1038/s41582-021-00486-9. Epub 2021 Apr 20. PMID: 33879872

Bestwick JP, Auger SD, Simonet C, Rees RN, Rack D, Jitlal M, et al. . Improving estimation of Parkinson's disease risk—the enhanced PREDICT-PD algorithm. NPJ Parkinsons Dis. (2021) 7:33. 10.1038/s41531-021-00176-9 - DOI - PMC - PubMed

Bohlken J Kostev K. [The *Influence of Caseload* on Continuous Treatment with Antidementia Drugs]. Fortschr Neurol Psychiatr. 2017 Mar;85(3):156-162. doi: 10.1055/s-0043-101233. Epub 2017 Mar 20. German. PMID:28320025

Bohlken J, Riedel-Heller S, Gothe H, Kostev K. Demenzprävention und hausärztliche Versorgung: Schätzung der Zielpopulation [Dementia prevention and primary care: Estimation of the target population]. Fortschr Neurol Psychiatr. 2021 German. doi: 10.1055/a-1227-6287. Epub ahead of print. PMID: 32877931

Bovolenta TM, de Azevedo Silva SM, Arb Saba R, Borges V, Ferraz HB, Felicio AC. Systematic Review and Critical Analysis of Cost Studies Associated with Parkinson's Disease. Parkinsons Dis. 2017;2017:3410946. doi: 10.1155/2017/3410946. Epub 2017 Mar 5. PMID: 28357150; PMCID: PMC5357537.

Breen DP, Evans JR, Farrell K, Brayne C, Barker RA. Determinants of delayed diagnosis in Parkinson's disease. J Neurol. 2013 Aug;260(8):1978-81. doi: 10.1007/s00415-013-6905-3. Epub 2013 Apr 10. PMID: 23572347.

Chen Y, Sun X, Lin Y, Zhang Z, Gao Y, Wu IXY. Non-genetic risk factors for Parkinson's disease: an overview of 46 systematic reviews. J Parkinsons Dis. (2021). [Epub ahead of print]. 10.3233/JPD-202521 - DOI - PubMed

Dommershuijsen LJ, Darweesh SKL, Luik AI, Kieboom BCT, Koudstaal PJ, Boon AJW, et al. . Ethical considerations in screening for rapid eye movement sleep behavior disorder in the general population. Mov Disord. (2020) 35:1939–44. 10.1002/mds.28262 - DOI - PubMed

Dommershuijsen LJ, Boon AJW, Ikram MK. Probing the Pre-diagnostic Phase of Parkinson's Disease in Population-Based Studies. Front Neurol. 2021 Jul 1;12:702502. doi: 10.3389/fneur.2021.702502. PMID: 34276552; PMCID: PMC8284316.

Eichler T, Thyrian JR, Hertel J, Michalowsky B, Wucherer D, Dreier A, Kilimann I, Teipel S, Hoffmann W. Rates of formal diagnosis of dementia in primary care: The effect of screening. Alzheimers Dement (Amst). 2015 Mar 29;1(1):87-93. doi: 10.1016/j.dadm.2014.11.007. PMID: 27239495; PMCID: PMC4876881.

Faust IM, Racette BA, Searles Nielsen S. Validation of a Parkinson Disease Predictive Model in a Population-Based Study. Parkinsons Dis. 2020 Feb 21;2020:2857608. doi: 10.1155/2020/2857608. PMID: 32148753; PMCID: PMC7054801.

Gan J, Wan Y, Shi J, Zhou M, Lou Z, Liu Z. A survey of subjective constipation in Parkinson's disease patients in shanghai and literature review. BMC Neurol. 2018 Mar 15;18(1):29. doi: 10.1186/s12883-018-1034-3. PMID: 29544459; PMCID: PMC5856226.

Gonera EG, van't Hof M, Berger HJ, van Weel C, Horstink MW. Symptoms and duration of the prodromal phase in Parkinson's disease. Mov Disord. 1997 Nov;12(6):871-6. doi: 10.1002/mds.870120607. PMID: 9399209.

Heinzel S, Berg D, Binder S, Ebersbach G, Hickstein L, Herbst H, Lorrain M, Wellach I, Maetzler W, Petersen G, Schmedt N, Volkmann J, Woitalla D, Amelung V. Do We Need to Rethink the Epidemiology and Healthcare Utilization of Parkinson's Disease in Germany? Front Neurol. 2018 Jun 29;9:500. doi: 10.3389/fneur.2018.00500. PMID: 30008693; PMCID: PMC6033992.

Hjalte F, Norlin JM, Kellerborg K, Odin P. Parkinson's disease in Sweden-resource use and costs by severity. Acta Neurol Scand. 2021 Jul 12. doi: 10.1111/ane.13502. Epub ahead of print. PMID: 34254292

Högl B, Stefani A, Videnovic A. Idiopathic REM sleep behaviour disorder and neurodegeneration — an update. Nat Rev Neurol. (2018) 14:40–55. 10.1038/nrneurol.2017.157 - DOI - PubMed

Kazmi H, Walker Z, Booij J, Khan F, Shah S, Sudre CH, Buckman JEJ, Schrag AE. Late onset depression: dopaminergic deficit and clinical features of prodromal Parkinson's disease: a cross-sectional study. J Neurol Neurosurg Psychiatry. 2021 Feb;92(2):158-164. doi: 10.1136/jnnp-2020-324266. Epub 2020 Dec 2. PMID: 33268471; PMCID: PMC7841491.

Mahlknecht P, Kiechl S, Stockner H, Willeit J, Gasperi A, Poewe W, Seppi K. Predictors for mild parkinsonian signs: a prospective population-based study. Parkinsonism Relat Disord. 2015 Mar;21(3):321-4. doi: 10.1016/j.parkreldis.2014.12.021. Epub 2014 Dec 31. PMID: 25585991.

Nerius M, Fink A, Doblhammer G. Parkinson's disease in Germany: prevalence and incidence based on health claims data. Acta Neurol Scand. 2017 Nov;136(5):386-392. doi: 10.1111/ane.12694. Epub 2016 Oct 10. PMID: 27726128; PMCID: PMC5655709.

Noyce AJ, Bestwick JP, Silveira-Moriyama L, Hawkes CH, Giovannoni G, Lees AJ, Schrag A. Meta-analysis of early nonmotor features and risk factors for Parkinson disease. Ann Neurol. 2012 Dec;72(6):893-901. doi: 10.1002/ana.23687. Epub 2012 Oct 15. PMID: 23071076; PMCID: PMC3556649.

Noyce AJ, R'Bibo L, Peress L, Bestwick JP, Adams-Carr KL, Mencacci NE, Hawkes CH, Masters JM, Wood N, Hardy J, Giovannoni G, Lees AJ, Schrag A. PREDICT-PD: An online approach to prospectively identify risk indicators of Parkinson's disease. Mov Disord. 2017 Feb;32(2):219-226. doi: 10.1002/mds.26898. Epub 2017 Jan

Noyce AJ, Schrag A, Masters JM, Bestwick JP, Giovannoni G, Lees AJ. Subtle motor disturbances in PREDICT-PD participants. J Neurol Neurosurg Psychiatry. 2017 Mar;88(3):212-217. doi: 10.1136/jnnp-2016-314524. Epub 2016 Dec 16. PMID: 27986830; PMCID: PMC5529958.

Noyce AJ, Lees AJ, Schrag AE. The prediagnostic phase of Parkinson's disease. J Neurol Neurosurg Psychiatry. 2016 Aug;87(8):871-8. doi: 10.1136/jnnp-2015-311890. Epub 2016 Jan 11. PMID: 26848171; PMCID: PMC4975823.

Plouvier AOA, Olde Hartman TC, Verhulst CEM, Bloem BR, van Weel C, Lagro-Janssen ALM. Parkinson's disease: patient and general practitioner perspectives on the role of primary care. Fam Pract. 2017 Apr 1;34(2):227-233. doi: 10.1093/fampra/cmw115. PMID: 28419289.

Poortvliet PC, O'Maley K, Silburn PA, Mellick GD. Perspective: Current Pitfalls in the Search for Future Treatments and Prevention of Parkinson's Disease. Front Neurol. 2020 Jul 8;11:686. doi: 10.3389/fneur.2020.00686. PMID: 32733372; PMCID: PMC7360677

Postuma RB, Berg D, Stern M, Poewe W, Olanow CW, Oertel W, Obeso J, Marek K, Litvan I, Lang AE, Halliday G, Goetz CG, Gasser T, Dubois B, Chan P, Bloem BR, Adler CH, Deuschl G. MDS clinical diagnostic criteria for Parkinson's disease. Mov Disord. 2015 Oct;30(12):1591-601. doi: 10.1002/mds.26424. PMID: 26474316.

Postuma RB, Berg D. Prodromal Parkinson's Disease: The Decade Past, the Decade to Come. Mov Disord. 2019 May;34(5):665-675. doi: 10.1002/mds.27670. Epub 2019 Mar 28. PMID: 30919499.

Rathmann W, Bongaerts B, Carius H-J, Kruppert S, Kostev K. Basic characteristics and representativeness of the German Disease Analyzer database. Int J Clin Pharmacol Ther. 2018;56: 459–466. doi:10.5414/CP203320

Rees RN, Acharya AP, Schrag A, Noyce AJ. An early diagnosis is not the same as a timely diagnosis of Parkinson's disease. F1000Res. 2018 Jul 18;7:F1000 Faculty Rev-1106. doi:

Rees RN, Noyce AJ, Schrag A. The prodromes of Parkinson's disease. Eur J Neurosci. 2019 Feb;49(3):320-327. doi: 10.1111/ejn.14269. Epub 2018 Dec 5. PMID: 30447019; PMCID: PMC6492156.

Reese JP, Hamer H, Oertel WH, Strzelczyk A, Mueller UO, Heilmaier C, Kostev K. Association of time-to-levodopa with initial Parkinsonian medication: a retrospective cohort study. Int J Clin Pharmacol Ther. 2015 Feb;53(2):107-14. doi: 10.5414/CP202230

Rosqvist K, Odin P, Lorenzl S, Meissner WG, Bloem BR, Ferreira JJ, Dodel R, Schrag A; Care of Late Stage Parkinsonism (CLaSP) Consortium. Factors Associated with Health-Related Quality of Life in Late-Stage Parkinson's Disease. Mov Disord Clin Pract. 2021 Mar 23;8(4):563-570. doi: 10.1002/mdc3.13186. PMID: 33981789; PMCID: PMC8088114.

Schrag A, Horsfall L, Walters K, Noyce A, Petersen I. Prediagnostic presentations of Parkinson's disease in primary care: a case-control study. Lancet Neurol. 2015 Jan;14(1):57-64. doi: 10.1016/S1474-4422(14)70287-X. Epub 2014 Nov 27. PMID: 25435387.

Schrag A, Anastasiou Z, Ambler G, et al. . Predicting diagnosis of Parkinson's disease: a risk algorithm based on primary care presentations. Mov Disord 2019;34:480–6.10.1002/mds.27616 - DOI - PMC - PubMed

Schrag A, Zhelev SS, Hotham S, Merritt RD, Khan K, Graham L. Heterogeneity in progression of prodromal features in Parkinson's disease. Parkinsonism Relat Disord. (2019) 64:275–9. 10.1016/j.parkreldis.2019.05.013 - DOI - PubMed

Searles Nielsen S, Warden MN, Camacho-Soto A, Willis AW, Wright BA, Racette BA. A predictive model to identify Parkinson disease from administrative claims data. Neurology. 2017 Oct 3;89(14):1448-1456. doi: 10.1212/WNL.0000000000004536. Epub 2017 Sep 1. PMID: 28864676; PMCID: PMC5631173.

Smedinga M, Darweesh SKL, Bloem BR, Post B, Richard E. Towards early disease modification of Parkinson's disease: a review of lessons learned in the Alzheimer field. J Neurol. (2020) 268:724–33. 10.1007/s00415-020-10162-5 - DOI - PMC - PubMed

Warda A, Reese JP, Tanislav C, Kostev K. The association between antihypertensive therapy and the incidence of Parkinson's disease in patients followed in general practices in Germany. Int J Clin Pharmacol Ther. 2019 Oct;57(10):483-488. doi: 10.5414/CP203559

Ygland Rödström E, Puschmann A. Clinical classification systems and long-term outcome in mid- and late-stage Parkinson's disease. NPJ Parkinsons Dis. 2021 Aug 2;7(1):66. doi: 10.1038/s41531-021-00208-4. PMID: 34341343; PMCID: PMC8329298.

Yilmaz R, Gräber S, Roeben B, Suenkel U, von Thaler AK, Heinzel S, Metzger FG, Eschweiler GW, Maetzler W, Berg D, Liepelt-Scarfone I. Cognitive Performance Patterns in Healthy Individuals with Substantia Nigra Hyperechogenicity and Early Parkinson's Disease. Front Aging Neurosci. 2016 Nov 15;8:271. doi: 10.3389/fnagi.2016.00271. PMID: 27895578; PMCID: PMC5108760

Yuan W, Beaulieu-Jones B, Krolewski R, Palmer N, Veyrat-Follet C, Frau F, Cohen C, Bozzi S, Cogswell M, Kumar D, Coulouvrat C, Leroy B, Fischer TZ, Sardi SP, Chandross KJ, Rubin LL, Wills AM, Kohane I, Lipnick SL. Accelerating diagnosis of Parkinson's disease through risk prediction. BMC Neurol. 2021 May 18;21(1):201. doi: 10.1186/s12883-021-02226-4. PMID: 34006233; PMCID: PMC8130278.

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

	Total		With ≥2 years of retrospective data		With ≥5 years of retrospective data		With ≥10 years of retrospective data	
	Parkinson'sdisease (n=17,702)	Controls (n=17,702)	Parkinson's disease (n=14,986)	Controls (n=15,708)	Parkinson's disease (n=10,378)	Controls (n=12,335)	Parkinson's disease (n=5,591)	Controls (n=6,440)
Sex								
Female	48.1	48.1	47.7	47.9	46.6	47.7	46.7	47.1
Male	51.9	51.9	52.3	52.1	53.4	52.3	53.3	52.9
Age at index date (mean, SD)	74.9 (10.2)	74.9 (10.2)	75.0 (10.1)	75.0 (10.1)	75.2 (9.9)	75.2 (9.9)	75.7 (9.7)	75.6 (9.9)

Table 2. Number of patients with symptoms prior to diagnosis or index date

	Within 0 to <2 years		≥2 years to <5 years		≥5 years to <10 years	
	Parkinson's disease (n=14,986)	Controls (n=15,708)	Parkinson's disease (n=10,378)	Controls (n=12,335)	Parkinson's disease (n=5,591)	Controls (n=6,440)
Motor dysfunctions						
Tremor	1,660 (11%)	277 (2%)	752 (7%)	256 (2%)	429 (8%)	223 (3%)
Rigidity	91 (1%)	50 (0%)	70 (1%)	45 (0%)	50 (1%)	57 (1%)
Balance impairment	1,569 (10%)	540 (3%)	661 (6%)	246 (2%)	170 (3%)	62 (1%)
Shoulder pain or stiffness	1,002 (7%)	754 (5%)	921 (9%)	638 (5%)	679 (12%)	575 (9%)
Neck pain or stiffness	981 (7%)	668 (4%)	966 (9%)	652 (5%)	746 (13%)	669 (10%)
Psychiatric disorders						
Depression	3,735 (25%)	1,709 (11%)	2,696 (26%)	1,302 (11%)	1,766 (32%)	1,132 (18%)
Anxiety	902 (6%)	466 (3%)	685 (7%)	338 (3%)	475 (8%)	308 (5%)
Memory problems	712 (5%)	252 (2%)	359 (3%)	160 (1%)	107 (2%)	44 (1%)
Insomnia	1,938 (13%)	1,152 (7%)	1,546 (15%)	937 (8%)	1,072 (19%)	775 (12%)
Autonomic dysfunction and fatigue						
Constipation	1,769 (12%)	743 (5%)	1,070 (10%)	464 (4%)	595 (11%)	286 (4%)
Hypotension	459 (3%)	226 (1%)	343 (3%)	149 (1%)	249 (4%)	171 (3%)
Urinary dysfunction	1114 (7%)	445 (3%)	669 (6%)	313 (3%)	278 (5%)	198 (3%)
Erectile dysfunction	170 (1%)	133 (1%)	189 (2%)	149 (11%)	182 (3%)	150 (2%)
Dizziness	2,367 (16%)	1,175 (7%)	1,758 (17%)	982 (8%)	1,032 (18%)	750 (12%)
Fatigue	1,058 (7%)	507 (3%)	638 (6%)	357 (3%)	357 (6%)	311 (5%)

Table 3. Odds Ratios of symptom presentations 2, 5, and 10 years prior to diagnosis/index date

	Within 0 to <2 years		≥2 years to <5 years		≥5 years to <10 years	
	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value
Motor dysfunctions						
Tremor	6.42 (5.61—7.35)	<0.001	3.24 (2.77—2.78)	<0.001	2.44 (1.98—3.02)	<0.001
Rigidity	1.68 (1.16—2.42)	0.006	1.49 (0.98—2.26)	0.061	1.45 (0.91—2.33)	0.122
Balance impairment	3.47 (3.11—3.87)	<0.001	3.28 (2.77—3.88)	<0.001	2.99 (2.08—4.29)	<0.001
Shoulder pain or stiffness	1.34 (1.21—1.49)	<0.001	1.62 (1.44—1.81)	<0.001	1.53 (1.32—1.77)	<0.001
Neck pain or stiffness	1.58 (1.42—1.76)	<0.001	1.68 (1.50—1.88)	<0.001	1.52 (1.33—1.75)	<0.001
Psychiatric disorders						
Depression	2.56 (2.40—2.73)	<0.001	2.41 (2.23—2.61)	<0.001	2.12 (1.91—2.36)	<0.001
Anxiety	2.04 (1.81—2.30)	<0.001	2.20 (1.90—2.54)	<0.001	1.89 (1.56—2.28)	<0.001
Memory problems	3.04 (2.60—3.55)	<0.001	2.59 (2.09—3.20)	<0.001	2.39 (1.57—3.65)	<0.001
Insomnia	1.80 (1.66—1.96)	<0.001	1.85 (1.68—2.04)	<0.001	1.86 (1.64—2.11)	<0.001
Autonomic dysfunction and fatigue						
Constipation	2.49 (2.27—2.74)	<0.001	2.53 (2.23—2.86)	<0.001	3.14 (2.58—3.82)	<0.001
Hypotension	2.28 (1.91—2.72)	<0.001	2.43 (1.96—3.02)	<0.001	1.83 (1.41—2.37)	<0.001
Urinary dysfunction	2.64 (2.34—2.97)	<0.001	2.24 (1.92—2.61)	<0.001	1.80 (1.42—2.29)	<0.001
Erectile dysfunction	1.25 (099—1.59)	0.066	1.43 (1.23—1.82)	0.003	1.47 (1.11—1.94)	0.007
Dizziness	2.31 (2.14—2.50)	<0.001	2.11 (1.92—2.31)	<0.001	1.85 (1.62—2.10)	<0.001
Fatigue	2.35 (2.09—2.65)	<0.001	2.11 (1.82—2.45)	<0.001	1.46 (1.20—1.78)	<0.001

Figure 1: Prevalence of motor symptoms of Parkinson's disease

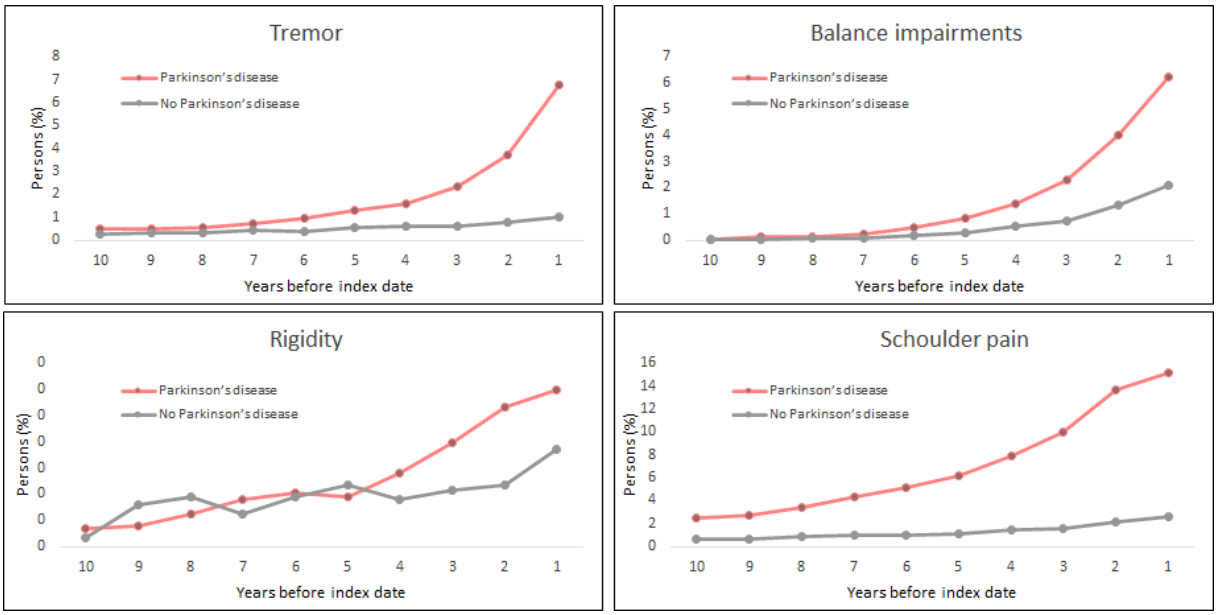

Figure 2: Prevalence of neuropsychiatric symptoms and insomnia

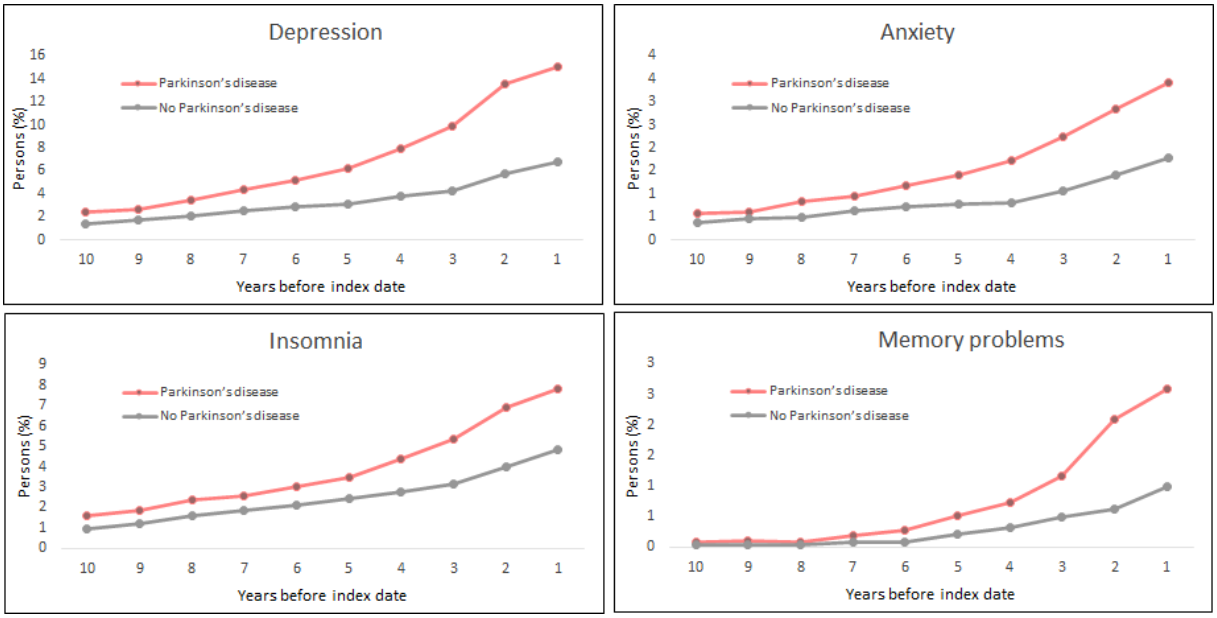

Figure 3: Prevalence of autonomic symptoms and fatigue