Title
Cognitive Impairment and Mortality in a Population-Based Parkinson’s Disease Cohort

Journal
Journal of Parkinson's Disease, Preprint(Preprint)

ISSN
1877-7171

Authors
Keener, Adrienne M
Paul, Kimberly C
Folle, Aline
et al.

Publication Date
2018

DOI
10.3233/jpd-171257

Peer reviewed

HHS Public Access

Author manuscript

J Parkinsons Dis. Author manuscript; available in PMC 2019 December 20.

Published in final edited form as:

J Parkinsons Dis. 2018 ; 8(2): 353–362. doi:10.3233/JPD-171257.

Cognitive Impairment and Mortality in a Population-Based Parkinson's Disease Cohort

Adrienne M. Keener[a,c], **Kimberly C. Paul**[b], **Aline Folle**[b], **Jeff M. Bronstein**[a], **Beate Ritz**[a,b,*]

[a]Department of Neurology, David Geffen School of Medicine, Los Angeles, CA, USA

[b]Department of Epidemiology, UCLA Fielding School of Public Health, Los Angeles, CA, USA

[c]Department of Neurology, Veterans Administration Greater Los Angeles Healthcare System, Los Angeles, CA, USA

Abstract

Background: Parkinson's disease (PD) is a heterogeneous disorder with variability in phenotype and progression.

Objective: We describe characteristics of PD patients in the largest population-based cohort followed for progression to date, and evaluate clinical risk factors for cognitive impairment and mortality.

Methods: We collected longitudinal data using the Unified Parkinson's Disease Rating Scale (UPDRS), Mini-Mental State Exam (MMSE), and Geriatric Depression Scale (GDS) in 242 new-onset PD patients followed for progression. We compared those who developed cognitive impairment (MMSE ≤ 24) with those who did not, using *t*-tests, chi-square tests, and Cox proportional hazards regression. Mortality risk factors were assessed in all 360 patients enrolled at baseline.

Results: Thirty-four patients developed cognitive impairment during follow-up. Baseline characteristics predictive of faster time to cognitive impairment were older age at diagnosis, fewer years of education, and longer average sleep duration reported. The 197 patients who died were older at diagnosis, reported longer average sleep duration, had lower baseline MMSE scores, higher UPDRS-III scores, and a higher proportion were of the postural instability gait difficulty (PIGD) subtype. Patients with the tremor dominant (TD) subtype at baseline were less likely to develop cognitive impairment or die during follow-up. Progression of cognitive, depressive, and motor symptoms occurred in parallel.

Conclusions: Motor symptom severity and subtype influence the incidence of cognitive impairment and mortality in PD, with the TD motor subtype being relatively protective. In addition, we newly found that longer average sleep duration at baseline predicts faster progression to cognitive impairment and mortality.

*Correspondence to: Beate Ritz, MD, PhD, UCLA, Epidemiology, Box 951772, Los Angeles, CA 90095, USA. Tel.: +1 310 206 7438; Fax: +1 310 206 6039; britz@ucla.edu.

Keywords

Parkinson's disease; disease progression; cognition; mortality; sleep

INTRODUCTION

Idiopathic Parkinson's disease (PD) is a clinically heterogeneous disorder, with variability in symptoms and disease progression. Recently, there has been increased awareness of the wide range of non-motor symptoms of PD, including cognitive impairment, and their contribution to disease phenotype. Dementia prevalence estimates in PD patients are much higher than in unaffected individuals, affecting up to 80% [1,2]. Cognitive impairment is known to negatively impact quality of life in PD patients, and is an independent risk factor for nursing home placement and mortality [3, 4].

Among the few identified clinical risk factors for dementia are older age, motor symptom severity, cognitive function at diagnosis, and the presence of visual hallucinations [2, 5]. Motor subtype also has implications for cognitive symptom progression, with the postural instability gait difficulty (PIGD) subtype increasing the risk of dementia [2]. Identifying early factors that characterize patients who later develop cognitive impairment may shed light on the underlying disease pathophysiology, encourage neuroprotective interventions, and allow clinicians to provide prognostic information and guidance for patients and their families.

The majority of PD progression studies to date rely on clinical patient cohorts that may not be representative of the PD population as a whole; drawing from tertiary referral centers or volunteers for clinical research trials. Of population-based PD progression studies, most have relied on prevalent patients with variable disease duration [6–12], which raises issues of survival or participation bias, especially when the goal is to study cognitive impairment and dementia.

Here we present results from a large population-based longitudinal study of new-onset PD patients, with the aim of identifying clinical risk factors for cognitive decline and mortality.

MATERIALS AND METHODS

The University of California, Los Angeles (UCLA) Institutional Review Board approved all study phases. Participants were informed of the study procedures and their rights, and provided written informed consent (or their legal guardian, whenever participants lacked cognitive ability to consent).

Study subjects

The Parkinson's Environment and Genes (PEG) Study was originally designed as a population-based case control study in Central California. As described previously [13], new-onset PD patients were recruited via contact with neurologists, large medical groups and public service announcements from 2001 to 2007. Patients were eligible if they met the following criteria: initially diagnosed with PD within 3 years of enrollment; resident of

Fresno, Tulare or Kern counties and living in California for at least 5 years; a UCLA Movement Disorders specialist (JB or colleagues) confirmed a diagnosis of probable (met 1 to 4 below) or possible (at least one sign from criterion 1 and met criteria 2 and 3) idiopathic PD clinically according to the following criteria [14, 15]: 1. manifestation of at least two signs: rest tremor, bradykinesia or cogwheel rigidity; 2. no suggestion of parkinsonian syndrome due to trauma, brain tumor, infection, cerebrovascular disease, other known neurological disease, or treatment with dopamine-blocking or dopamine-depleting agents; 3. no atypical features (such as prominent oculomotor palsy, cerebellar signs, vocal cord paresis, severe orthostatic hypotension, pyramidal signs, amyotrophy or limb apraxia); 4. asymmetric onset; 5. symptomatic improvement if treated with levodopa. Additionally, eligible patients did not have a diagnosis of neurological or serious psychiatric disorders (including bipolar disorder, schizophrenia, or dementia before motor symptom onset), were not terminally ill, and were willing to participate. At baseline, we excluded 5 PD patients with dementia and 7 patients with a likely diagnosis of dementia with Lewy-body.

The study interviewed and examined 373 PD patients at baseline, 81% of all the potentially eligible PD patients identified for the PEG case-control study [16]. In 2007, on average 3.5 years after their baseline exam (SD = 1.9 years), these patients were invited fora follow-up investigation; 70 patients were dead or too ill, 17 withdrew, and 21 could not be re-contacted. Among 265 we re-examined, 13 were found not to have idiopathic PD; and 10 patients could not be assessed cognitively at follow-up, leaving 242 patients for analyses. We conducted a third exam for 192 of these patients, on average 2.2 years later (SD = 0.5), though only 179 participated in a third MMSE evaluation (see Fig. 1). For mortality analyses we relied on all PD patients who remained in the idiopathic category during follow-up (n = 360) with vital status assessed last in July 2016.

Data collection and measures

Patients were assessed by UCLA neurologists and trained staff at a local facility or patients' home to confirm diagnoses and evaluate clinical features using the Unified Parkinson's Disease Rating Scale (UPDRS). Patients were preferably examined while off PD medications, at least 12 hours after their last dose. For patients who were not off medication (18% at baseline, 20% at follow-up), we estimated off-scores by adding the whole study population's mean off- and on-score difference to the patient's on-score [16]. Trained interviewers measured blood pressure, height and weight, administered the Mini-Mental State Exam (MMSE) and the Geriatric Depression Scale (GDS 15-point short form) and recorded co-morbidities and medication use, as well as demographic and lifestyle information, including average hours of sleep during young adult, adult, middle, and senior age. PD duration was recorded as the time since first doctor's diagnosis of PD. We repeated the UPDRS, GDS, MMSE, and collected medical and lifestyle data during follow-up visits.

Cognitive Impairment was defined as having an intermediate/normal baseline MMSE score (>24) and a follow-up MMSE score of ≤24.

UPDRS-III, PD subtype, motor progression

Sub-scores for tremor, bradykinesia, rigidity, and postural reflex impairment were calculated based on published guidelines [17]. PD motor subtypes (tremor dominant (TD), postural instability gait difficulty (PIGD), or indeterminate (IND)) were defined by the Standardized Tremor: PIGD Ratio, i.e. the ratio of the mean UPDRS tremor scores to the mean PIGD scores [18]. Fast motor progression was defined as a 5 points or more increase in the annual UPDRS motor score [16]. Levodopa (LD) and equivalent (LED) dose were calculated based on published guidelines [19].

Depression

Depression was defined as a GDS score of 7 or greater [20]. We previously reported high sensitivity and positive predictive values for the GDS compared with the Structured Clinical Interview for DSM Disorders (SCID) and the Patient Health Questionnaire (PHQ-9) [21].

Survival

Continued mortality surveillance has been carried out during follow-up, through contact with relatives, matching of social security numbers to vital statistics data, and review of public obituaries; we obtained death certificates for everyone.

Statistical analysis

We provide demographic and clinical characteristics for PD patients with/out cognitive impairment, and patients who did/did not die during follow-up. Chi-square and *t*-tests were applied to assess unadjusted mean between-group differences for demographic information, comorbidities such as heart disease, stroke, and diabetes, medication use, blood pressure and body mass index (BMI), in addition to PD symptom scores.

Using Cox's proportional hazards regression, we examined associations between patient characteristics and baseline PD motor/non-motor symptom scores and time to exam when cognitive impairment was measured (34 events, 190 patients censored) and time to death (197 events, 163 patients censored). Patients with cognitive impairment at baseline (N = 18) were excluded from models of cognitive impairment. We controlled for potential confounders including age at diagnosis, sex, ethnicity, education, and cigarette smoking. We tested the validity of the proportional hazards assumption for each predictor using a Kolmogorov-type supremum test based on 1,000 simulated residual patterns. For predictors for which the proportionality assumption failed ($p < 0.05$; for education, UPDRS-III, Bradykinesia Score, Postural Reflex Impairment Score, MMSE, GDS, and stroke for mortality analysis), we included an interaction term between the predictor and time (Allison, 1995). Given the large number of tests we performed, we also provide a false discovery rate adjusted *p*-value for each association measure. All analyses were completed with SAS 9.4 (SAS Institute Inc., Cary, NC).

RESULTS

Of the 360 PD patients, the 70 who were dead or too ill prior to follow-up had a similar average disease duration at enrollment (0.9 years), but were older at diagnosis, smoked more

pack-years of cigarettes, and while fewer reported taking aspirin or NSAIDS, more reported a history of stroke and heart attack (Table 1). Those (38, 11%) lost to follow-up were quite similar to those we followed in terms of demographics, health indicators, and PD symptom levels at baseline, except for having a higher diastolic BP, less aspirin use, and a higher proportion with PIGD motor sub-type (Table 1). Among the 197 patients deceased as of July 2016, those with follow-up exams had a mean follow-up of 5.8 years (SD = 2.1) and average disease duration of 7.2 years (SD = 2.8). Tables 1 and 2 display the Mean (SD) of continuous variables, Supplementary Table 1 displays the Median (Range) of the same variables.

Characteristics of patients who developed cognitive impairment

Among the 224 cognitively normal patients with follow-up exams, 34 developed incident cognitive impairment (MMSE ≤ 24). The mean PD duration (time since diagnosis) when we detected impairment was 6.8 years. Patients who developed cognitive impairment were slightly older at diagnosis than those who did not (69.0 vs. 66.2); otherwise they were similar in demographics, except that more with non-European ancestry developed cognitive impairment. At baseline, patients who developed cognitive impairment were similar in terms of medical history, including stroke, heart attack, medication use (aspirin, NSAIDs), and average hours of sleep over lifetime and within 10 years prior to baseline exam (Table 1).

Patients who developed cognitive impairment during follow-up already had significantly lower MMSE scores at baseline (Table 2: 27.9 vs. 28.7), and their mean score difference continued to grow (21.4 at last follow-up vs. 28.1; Fig. 2A, trend test $p < 0.0001$). Mean GDS scores were similar at baseline; however, by the end of follow-up, those with incident cognitive impairment had significantly higher GDS scores (Table 2; Fig. 2B, trend test $p = 0.03$).

Motor progression, measured with the UPDRS-III, mirrored cognitive decline. Those who developed cognitive impairment started from slightly higher baseline motor scores (27.9 vs. 28.7), with a statistically significantly difference for postural reflex impairment items (Table 2). Throughout follow-up, motor scores, except for tremor, progressed faster in the cognitively impaired group (Table 2; Fig. 2C, trend test $p < 0.0001$, and 2D), and the proportion of PIGD subtype patients was higher. Motor symptom severity is also reflected in higher daily levodopa use at baseline and throughout follow-up among those who developed cognitive impairment (Table 2). Overall, those who developed cognitive impairment on average declined more than 6 points on the MMSE, gained 3 points on the GDS and developed depression (44% vs. 27%), and gained 22 points on the UPDRS-III (fast motor progressors: 39% vs. 11%); these differences between those who did/did not develop cognitive impairment were statistically significant (Table 3).

Characteristics of patients who died over follow-up

The 197 patients who died were older at diagnosis, had smoked more pack-years of cigarettes, and were more affected by stroke and heart attacks compared with those alive at end of follow-up (right censored) (Table 1). However, at baseline, they had a lower diastolic

BP and BMI, a higher proportion were taking BP medications, and the average hours of sleep they reported over their lifetime was higher (Table 1).

Patients who died had similar PD duration at time of their baseline exam (1.2 years), but presented with slightly lower MMSE (27.3 vs. 28.2) and higher UPDRS-III scores (23.7 vs. 18.6), and a higher proportion had the PIGD motor subtype at baseline. This pattern became even more pronounced during follow-up (MMSE: 25.9 vs. 27.6; UPDRS-III: 34.6 vs. 27.7). Depression was also associated with mortality; those who died had a higher GDS score at final exam (4.9 vs. 3.7). Patients who died during follow-up had a steeper decline on the MMSE (2.07 vs. 0.51 points) and increases on the GDS (1.84 vs. 0.32 points) and UPDRS-III (13.8 vs. 9.4 points) relative to those who were alive and censored at end of follow-up (Table 3).

Predictors of time to cognitive impairment and mortality

The mean PD duration at the time of exam when we detected cognitive impairment was 6.8 years (SD = 2.3), 5.9 years (SD = 2.2) after the baseline exam (Table 2). Older age at diagnosis, fewer years of education, and longer average sleep duration were the only baseline characteristics predictive of faster time to cognitive impairment (Table 4). Among sleep patterns, higher average hours of sleep over their lifetime (HR = 1.57, 95% CI = 1.02–2.42) and within the 10 years prior to PD diagnosis (HR = 1.33, 95% CI= 1.02–1.41) were associated with faster time to cognitive impairment. In terms of PD symptoms and characteristics, longer disease duration at baseline, lower baseline MMSE score, and higher baseline postural reflex impairment UPDRS-III sub-score were predictive of faster time to cognitive impairment (Table 4). In contrast, patients presenting at baseline with the tremor dominant (TD) PD subtype were protected from developing cognitive impairment (HR = 0.21, 95% CI = 0.05, 0.91); for those of indeterminate subtype we estimated a negative association relative to the PIGD subtype (HR = 0.37, 95% CI = 0.06, 2.14) but the 95%CI included the null value (Table 4).

In our cohort, the average disease duration at death was 7.1 years (SD = 3.7), 5.8 years (SD = 3.3) after enrollment. Older age at PD diagnosis, ever smoking, a higher number of smoking pack-years, history of stroke and heart attack, and longer average sleep duration i were all associated with faster time to mortality (Table 4). Importantly, nearly all baseline symptom scores were associated with faster time to mortality (Table 4), including MMSE, GDS, and UPDRS-III scores, and all motor sub-scores. Tremor dominant (TD) and indeterminate subtype patients at baseline exhibited reduced mortality (HR = 0.58, 95% CI = 0.38, 0.88 and HR = 0.57, 95% CI = 0.32, 1.00) relative to those with the PIGD subtype (Table 4).

We have also included sensitivity analysis, running time to cognitive impairment and mortality, only adjusting for age and baseline MMSE score. These results can be found in Supplementary Table 2.

DISCUSSION

In this prospective, population-based study, the largest cohort of community-based Parkinson's disease patients with in-person examination by movement disorder specialists and serial cognitive assessments in the literature to date, we have confirmed previous reports and newly identified several clinical risk factors for the development of cognitive decline and mortality in PD, including lower baseline MMSE score, greater motor symptom severity, PIGD motor subtype, and longer reported average sleep duration prior to diagnosis.

In our population, motor symptom progression mirrored cognitive decline. By the end of follow-up, these patients showed more advanced motor scores across the UPDRS-III, with the exception of tremor. At baseline, the postural reflex impairment score, which includes axial symptoms such as posture, gait, and postural stability, was the only sub-score predictive of cognitive decline and mortality. This was confirmed in our Cox regression analyses, where baseline PIGD motor subtype was associated with a faster time to development of cognitive impairment and time to mortality relative to the TD subtype.

Previous epidemiologic studies have shown that the PIGD motor subtype is associated with cognitive decline and mortality [22–24]. Similar to our own study, a UK study enrolled and reported on patterns of progression in a representative sample of community-based PD patients who were followed from early in diagnosis [5]. In that study, 142 PD patients were followed for 7.2 years on average after diagnosis at which time 55% had died, 68% had postural instability and 46% developed dementia [5]. In this UK cohort, the TD subtype protected against progression to HY-stage 3, but an association between motor subtype and progression to dementia was not seen, possibly due to sample size limitations [5]. Furthermore, in contrast to our study, their patients were assessed while 'on' PD medication, which may have limited motor symptom and subtype assessment.

Our findings provide evidence, in a population-based cohort of PD patients, that the PIGD motor subtype tracks progression of the non-motor features of cognitive impairment and depression. Together, this characterizes a distinct PD subtype with faster disease progression and higher mortality. This corroborates a smaller recent study that applied a cluster analysis approach to describe this phenotype of PD as 'diffuse/malignant'; with higher rates of cognitive impairment and gait difficulties at baseline, and more rapid progression in all domains over a 4.5-year follow up period [25]. The Oxford Discovery cohort (N = 155) revealed similar findings, with the development of cognitive impairment at 18-months follow-up associated with worse motor and non-motor features of PD, suggesting a 'faster progressive phenotype' [26].

Sleep problems are common non-motor symptoms in PD, with REM sleep behavior disorder known to be associated with PD incidence and with cognitive impairment in PD [27]. Sleep duration has been associated with cognitive decline and mortality in older populations in general [28], and one study has reported that longer sleep duration is associated with Parkinson's disease incidence [29], but our study is the first to evaluate the implications of sleep duration on PD progression. Our results are consistent with reports in other patient populations, in that self-reported average sleep duration in the ten years prior to baseline was

positively associated with faster cognitive decline and higher mortality [28]. Additionally, associations with cognitive decline slightly strengthened (HR = 1.65; 95% CI 1.09,2.49, p = 0.02) among participants who reported seven or more hours of average sleep, i.e. when we excluded those with very little average sleep. These associations persisted when we adjusted for baseline UPDRS-III score and PD subtype, indicating that a measure as simple as average sleep duration in the years prior to diagnosis may be clinically relevant as an independent predictor of cognitive decline in PD.

Among the main strengths of this study are the new-onset, population-based nature of the cohort, one of few worldwide and the largest to date. Patients were assessed in person in a standardized manner 'off' medication by UCLA Movement Disorder neurologists. The population-based selection of patients from the tri-county California region allowed us to study the natural course of disease progression in a representative sample of PD patients. This is inherently different from studying selected tertiary care patients. Further, most progression studies, including some population-based ones, have relied on prevalent patients with varying disease duration, raising concerns about survival or participation bias.

All 360 patients enrolled in the cohort were assessed for mortality throughout follow-up and included in analyses aimed to identify baseline predictors. However, 70 patients were too ill/died and 38 withdrew or could not be re-contacted before cognitive outcomes could be re-assessed at follow-up. This is similar to the loss to follow-up seen in other longitudinal population-based studies of PD [5,30]. As seen in Tables 1 and 2, loss to follow-up from death or illness was related to several characteristics under study, including lower MMSE, higher UPDRS-III, and the PIGD subtype to name a few. Given these factors are positively associated with both loss to follow-up and cognitive impairment or mortality; this may have led to a substantial underestimation of associations.

By evaluating various motor and non-motor symptoms over time, our data demonstrate that disease progression in PD is experienced in multiple domains simultaneously, with a more rapidly progressive phenotype emerging, characterized by PIGD motor subtype, cognitive impairment, and depression. In addition, we newly identified longer reported sleep duration at baseline as an independent predictor of cognitive decline and mortality in PD, which may serve as a simple clinical measure that predicts poorer outcomes in PD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENTS

This work was supported by the National Institute of Health (NIEHS 2R01-ES010544, U54ES012078 and NINDS P50NS038367); a Burroughs Wellcome Fund training grant (KP); pilot funding was received from the SCEHSC # 5P30 ES07048 and The American Parkinson Disease Association.

CONFLICT OF INTEREST

Jeff M. Bronstein received support from the Veterans Administration Healthcare System (SW PADRECC), the Levine Foundation, and the Parkinson Alliance. Adrienne M Keener has received an American Parkinson Disease Association pilot award. Kimberly C Paul received a Burroughs Wellcome Fund training grant.

REFERENCES

[1]. Hely MA, Reid WGJ. Adena MA, Halliday GM, Morris JGL (2008) The Sydney Multicenter Study of Parkinson's disease: The inevitability of dementia at 20 years. Mov Disord 23, 837–844. [PubMed: 18307261]

[2]. Aarsland D, Kurz MW (2010) The epidemiology of dementia associated with Parkinson disease. J Neurol Sci 289, 18–22. [PubMed: 19733364]

[3]. Aarsland D, Larsen JP, Tandberg E, Laake K (2000) Predictors of nursing home placement in Parkinson's disease: A population-based, prospective study. J Am Geriatr Soc 48 938–942. [PubMed: 10968298]

[4]. Levy G, Tang M-X, Louis ED, Cote LJ, Alfaro B, Mejia H, Stem Y, Marder K (2002) The association of incident dementia with mortality in PD. Neurology 59, 1708–1713. [PubMed: 12473757]

[5]. Williams-Gray CH, Mason SL, Evans JR, Foltynie T, Brayne C, Robbins TW, Barker RA (2013) The CamPaIGN study of Parkinson's disease: 10-year outlook in an incident population-based cohort. J Neurol Neurosurg Psychiatry 84 1258–1264. [PubMed: 23781007]

[6]. Buter TC, van den Hout A, Matthews FE, Larsen JP, Brayne C, Aarsland D (2008) Dementia and survival in Parkinson disease: A 12-year population study. Neurol 70,1017–1022.

[7]. Hobson P. Meara J (2004) Risk and incidence of dementia in a cohort of older subjects with Parkinson's disease in the United Kingdom. Mov Disord 19, 1043–1049. [PubMed: 15372593]

[8]. Berger K, Breteler MM. Helmer C, Inzitari D, Fratiglioni L, Trenkwalder C, Hofman A, Launer LJ (2000) Prognosis with Parkinson's disease in europe: A collaborative study of population-based cohorts. Neurologic Diseases in the Elderly Research Group. Neurology 54 S24–S27. [PubMed: 10854358]

[9]. D'Amelio M, Ragonese P, Morgante L, Reggio A, Callari G, Salemi G, Savettieri G (2006) Long-term survival of Parkinson's disease: A population-based study. J Neurol 253, 33–37. [PubMed: 16021349]

[10]. De Lau LML, Schipper CMA, Hofman A. Koudstaal PJ. Breteler MMB (2005) Prognosis of Parkinson disease. Arch Neurol 62, 1265–1269. [PubMed: 16087767]

[11]. Fall PA, Saleh A, Fredrickson M, Olsson JE, Granerus AK (2003) Survival time, mortality, and cause of death in elderly patients with Parkinson's disease: A 9-year follow-up. Mov Disord 18, 1312–1316. [PubMed: 14639673]

[12]. Posada IJ, Benito-Leon J, Louis ED, Trincado R, Villarejo A, Medrano MJ, Bermejo-Pareja F (2011) Mortality from Parkinson's disease: A population-based prospective study (NEDICES). Mov Disord 26, 2522–2529. [PubMed: 21915906]

[13]. Kang GA, Bronstein JM, Masterman DL, Redelings M, Crum JA, Ritz B (2005) Clinical characteristics in early Parkinson's disease in a central California population-based study. Mov Disord 20, 1133–1142. [PubMed: 15954133]

[14]. Gelb DJ, Oliver E. Gilman S (1999) Diagnostic criteria for Parkinson disease. Arch Neurol 56, 33–39. [PubMed: 9923759]

[15]. Hughes AJ, Ben-Shlomo Y, Daniel SE, Lees AJ (1992) What features improve the accuracy of clinical diagnosis in Parkinson's disease: A clinicopathologic study. Neurology 42 1142–1146. [PubMed: 1603339]

[16]. Ritz B, Rhodes SL, Bordelon Y, Bronstein J (2012) alpha-Synuclein genetic variants predict faster motor symptom progression in idiopathic Parkinson disease. PLoS One 7, e36199. [PubMed: 22615757]

[17]. Louis ED, Tang MX, Cote L, Alfaro B, Mejia H, Marder K (1999) Progression of parkinsonian signs in Parkinson disease. Arch Neurol 56, 334–337. [PubMed: 10190824]

[18]. Stebbins GT, Goetz CG, Bum DJ, Jankovic J, Khoo TK, Tilley BC (2013) How to identify tremor dominant and postural instability/gait difficulty groups with the movement disorder society unified Parkinson's disease rating scale: Comparison with the unified Parkinson's disease rating scale. Mov Disord 28 668–670. [PubMed: 23408503]

[19]. Tomlinson CL, Stowe R, Patel S, Rick C, Gray R, Clarke CE (2010) Systematic review of levodopa dose equivalency reporting in Parkinson's disease. Mov Disord 25, 2649–2653. [PubMed: 21069833]

[20]. Burke WJ. Roccaforte WH, Wengel SP (1991) The short form of the Geriatric Depression Scale: A comparison with the 30-item form. J Geriatr Psychiatry Neurol 4, 173–178. [PubMed: 1953971]

[21]. Thompson AW. Liu H, Hays RD, Katon WJ, Rausch R, Diaz N, Jacob EL, Vassar SD, Vickrey BG (2011) Diagnostic accuracy and agreement across three depression assessment measures for Parkinson's disease. Park Relat Disord 17, 40–45.

[22]. Anang JBM, Gagnon J-F, Bertrand J-A, Romenets SR, Latreille V. Panisset M, Montplaisir J. Postuma RB (2014) Predictors of dementia in Parkinson disease: A prospective cohort study. Neurology 83, 1253–1260. [PubMed: 25171928]

[23]. De Lau LML, Verbaan D, van Rooden SM, Marinus J, van Hilten JJ (2014) Relation of clinical subtypes in Parkinson's disease with survival. Mov Disord 29 150–151. [PubMed: 24038593]

[24]. Kwon K-Y, Kang SH, Kim M, Lee HM, Jang JW, Kim JY, Lee S-M. Koh S-B (2014) Nonmotor Symptoms and Cognitive Decline in de novo Parkinson's Disease. Can J Neurol Sci 41 597–602. [PubMed: 25373810]

[25]. Fereshtehnejad S, Romenets S, Anang J, Latreille V, Gagnon JF, Postuma RB (2015) New clinical subtypes of Parkinson disease and their longitudinal progression. JAMA Neurol 72, El–11.

[26]. Hu MTM, Szewczyk-Krolikowski K, Tomlinson P. Nithi K. Rolinski M. Murray C, Talbot K, Ebmeier KP. Mackay CE, Ben-Shlomo Y (2014) Predictors of cognitive impairment in an early stage Parkinson's disease cohort. Mov Disord 29, 351–359. [PubMed: 24395708]

[27]. Gagnon JF, Vendette M, Postuma RB, Desjardins C, Massicotte-Marquez J, Panisset M, Montplaisir J (2009) Mild cognitive impairment in rapid eye movement sleep behavior disorder and Parkinson's disease. Ann Neurol 66, 39–47. [PubMed: 19670440]

[28]. Devore EE, Grodstein F, Schemhammer ES (2016) Sleep duration in relation to cognitive function among older adults: A systematic review of observational studies. Neuroepidemiology 46, 57–78. [PubMed: 26735553]

[29]. Chen H. Schemhammer E, Schwarzschild MA, Ascherio A (2006) A prospective study of night shift work, sleep duration, and risk of Parkinson's disease. Am J Epidemiol 163, 726–730. [PubMed: 16495472]

[30]. Alves G, Larsen JP, Emre M, Wentzel-Larsen T, Aarsland D (2006) Changes in motor subtype and risk for incident dementia in Parkinson's disease. Mov Disord 21, 1123–1130. [PubMed: 16637023]

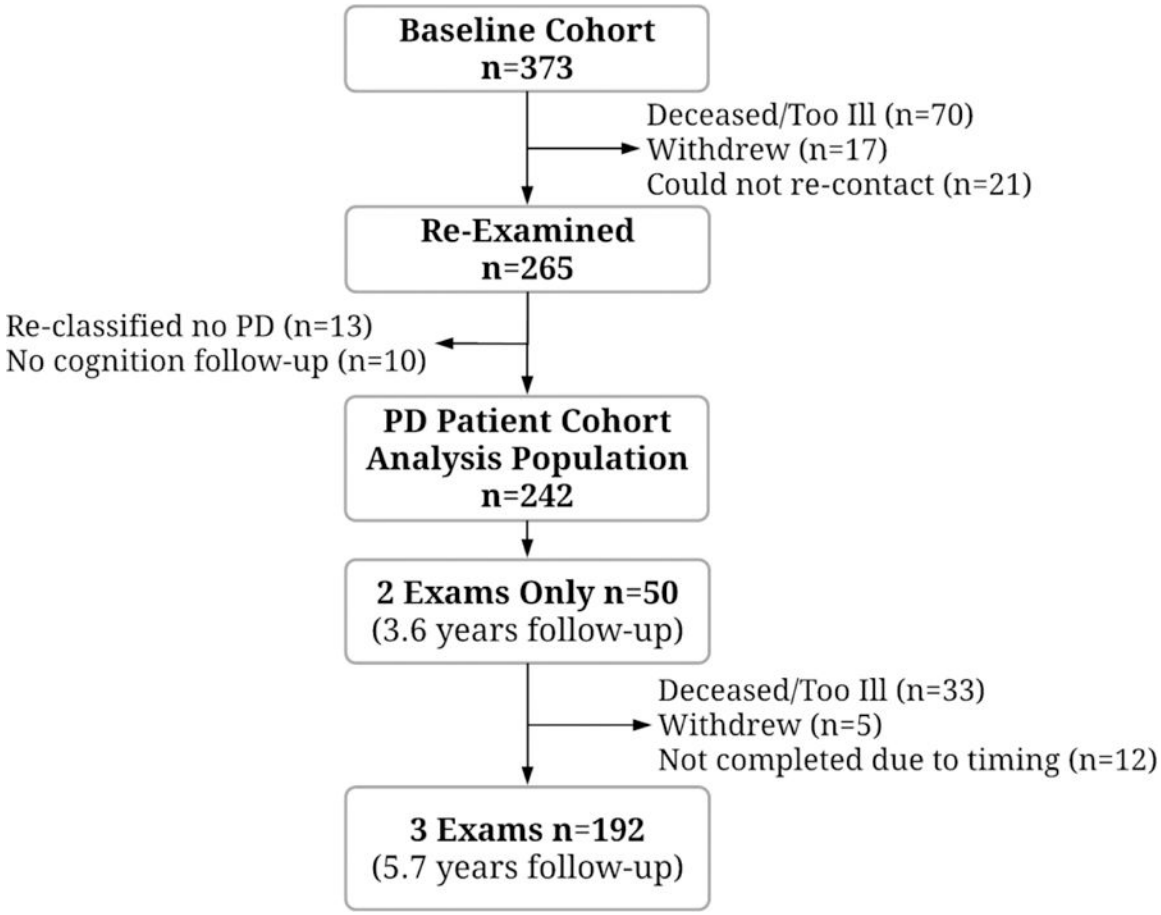

Figure 1.
Flow diagram of study participation.

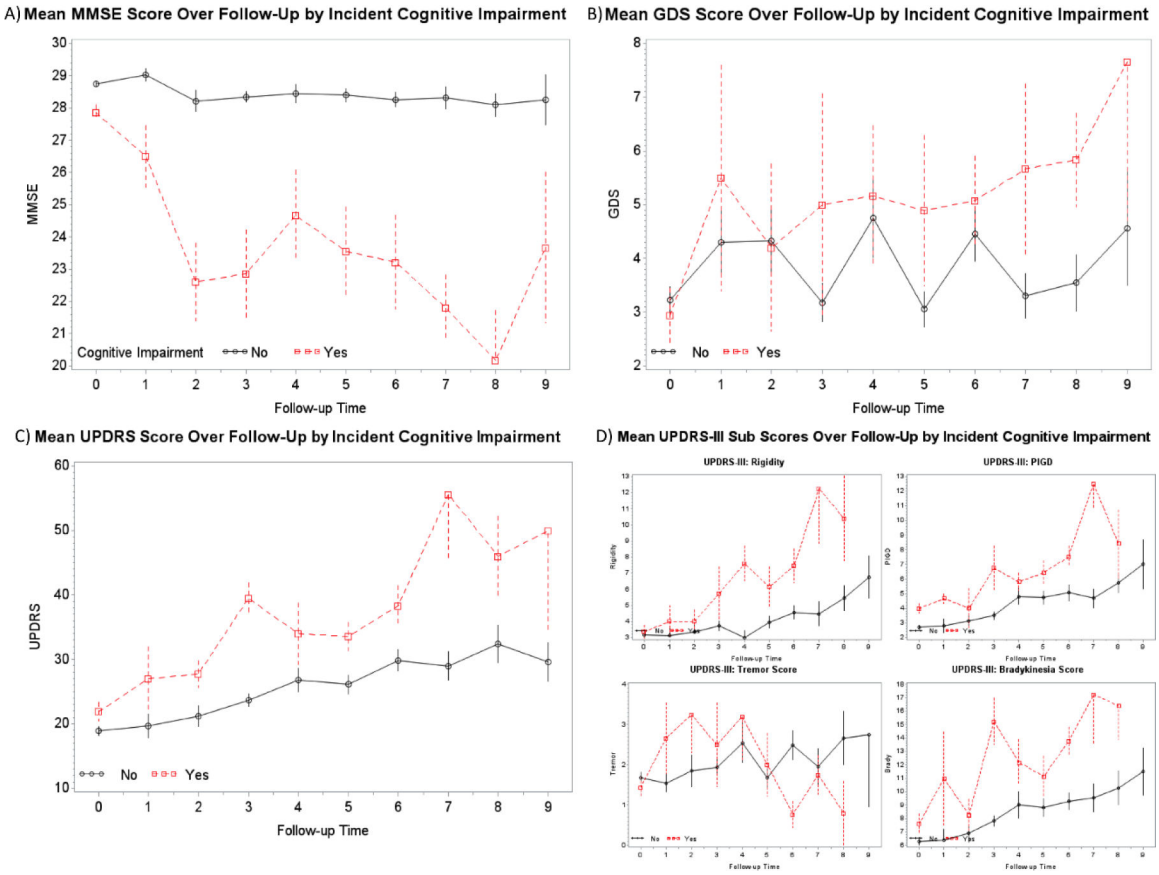

Figure 2.

Mean PD symptom exam scores over follow-up by incident cognitive impairment; A) MMSE – Cochran-Armitage Trend Test $P<.0001$; B) GDS – $P= 0.0282$; C) UPDRS- III – $P<.0001$; D) UPDRS-III Subscores: Tremor – $P=0.2423$, Bradykinesia – $P<.0001$, Rigidity – $P<.0001$, PIGD – $P<.0001$

J Parkinsons Dis. Author manuscript; available in PMC 2019 December 20.

Table 1.

Baseline characteristics by cognitive impairment and mortality in PEG cohort. See Supplemental Table 1 for the median and range of continuous variables

Characteristic:	**Baseline Cohort Enrolled (n=360)**			**Evaluated for Mortality (n=360)**		**Evaluated for Changes in Cognition during Follow-up[a] (n=242)**		
Mean (SD) or n (%)	**Follow-up Cohort (n=252)**	**Lost to Follow-up/ Deceased or Too-Ill[b] (n=70)**	**Lost to Follow-up/ Withdrew[b] (n=38)**	**Alive at end of Follow-up (n=163)**	**Deceased during follow-up[c] (n=197)**	**No/Mild Cognitive Impairment (N=190)**	**Incident Cognitive Impairment[d] (N=34)**	**Cognitive Impairment at Baseline[d] (n=18)**
Demographics								
Age at diagnosis	67.0 (9.9)	74.3 (5.9)*	66.1 (13.5)	62.8 (10.6)	72.8 (7.3)*	66.2 (9.8)	69.0 (10.4)	70.0 (9.8)
Sex, male	138 (57)	40 (57)	23 (61)	96 (59)	110 (56)	105 (55)	20 (59)	13 (72)
Non-European Ancestry	48 (20)	12 (17)	9 (24)	34 (21)	36 (18)	28 (15)	11 (32)*	9 (50)
Education, yrs	13.7 (4.4)	12.4 (3.2)*	13.6 (2.9)	13.8 (4.4)	13.1 (3.7)	14.3 (4.0)	13.1 (4.6)	9.0 (5.5)
Smoker, ever	110 (45)	35 (50)	21 (55)	70 (43)	102 (52)	87 (46)	16 (47)	7 (39)
Pack-years	9.9 (21.0)	16.1 (28.9)*	9.2 (13.1)	7.8 (16.0)	13.7 (26.1)*	9.9 (20.6)	9.7 (18.8)	4.2 (8.3)
Health Indicators								
Self-reported (Has patient ever been told by a doctor, they have…)								
Diabetes	31 (13)	10 (14)	5 (13)	17 (10)	32 (16)	26 (14)	3 (9)	2 (11)
Stroke	18 (7)	13 (19)*	4 (11)	11 (7)	25 (13)*	13 (6)	3 (9)	2 (11)
Heart Attack	20 (8)	12 (17)*	2 (5)	9 (5)	26 (13)*	17 (9)	2 (6)	1 (6)
High BP	129 (53)	32 (46)	19 (50)	81 (50)	104 (53)	101 (53)	15 (44)	13 (72)
Measured								
Systolic BP	134.2 (22.4)	135.6 (19.5)	140.3 (24.0)	134.0 (23.0)	136.1 (21.4)	135.0 (21.8)	130.4 (29.6)	132.8 (21.3)
Diastolic BP	76.7 (13.9)	74.4 (11.9)	86.2 (23.6)*	80.2 (18.0)	74.8 (12.0)*	76.8 (12.0)	76.1 (23.4)	76.3 (10.7)
BMI	27.3 (4.7)	25.9 (5.2)*	27.1 (5.8)	27.7 (5.4)	26.3 (4.8)*	27.3 (5.3)	27.7 (4.0)	27.2 (4.5)
Medication Use								
Aspirin, ever use	105 (43)	18 (25)*	9 (24)*	66 (40)	70 (36)	83 (44)	15 (44)	7 (39)
2+ years of us	88 (36)	15 (21)*	9 (24)	55 (34)	59 (30)	69 (36)	14 (41)	5 (28)
NSAIDs, ever use	64 (26)	10 (14)*	10 (26)	46 (28)	40 (20)	55 (29)	7 (21)	2 (11)
2+ years of use	48 (20)	7 (10)	8 (21)	34 (21)	30 (15)	41 (21)	5 (15)	2 (11)
BP Meds, ever use	141 (59)	40 (58)	19 (50)	83 (52)	122 (62)*	111 (59)	20 (59)	7 (59)

Characteristic:	Baseline Cohort Enrolled (n=360)			Evaluated for Mortality (n=360)		Evaluated for Changes in Cognition during Follow-up[a] (n=242)		
Mean (SD) or n (%)	Follow-up Cohort (n=252)	Lost to Follow-up/ Deceased or Too-Ill[b] (n=70)	Lost to Follow-up/ Withdrew[b] (n=38)	Alive at end of Follow-up (n=163)	Deceased during follow-up[c] (n=197)	No/Mild Cognitive Impairment (N=190)	Incident Cognitive Impairment[d] (N=34)	Cognitive Impairment at Baseline[d] (n=18)
Average Sleep Levels, hours								
Lifetime	7.2 (1.5)	7.5 (1.5)	7.0 (1.1)	7.0 (1.5)	7.4 (1.4)*	7.3 (0.9)	7.3 (1.0)	6.5 (1.2)
10 years prior to interview	7.3 (1.0)	7.3 (0.94)	7.3 (0.95)	7.2 (1.1)	7.3 (0.9)	7.2 (1.4)	7.3 (1.5)	6.2 (1.4)

*p<0.05, based on chi-square or t-test

Abbreviations: BP=blood pressure; BMI=body mass index; NSAIDs=nonsteroidal anti-inflammatory drugs

[a]Excludes10 participants who did not complete MMSE during follow-up

[b]Compared with those with follow-up (whole cohort, n=252)

[c]Includes patients who died before follow-up exams

[d]Compared with those who were censored at last ascertainment (2016)

J Parkinsons Dis. Author manuscript; available in PMC 2019 December 20.

Table 2.

Baseline PD characteristics and symptom scores by cognitive impairment and mortality in PEG cohort.

	Baseline Cohort Enrolled (n=360)			Evaluated for Mortality (n=360)		Evaluated for Changes in Cognition during Follow-up[a] (n=242)		
PD Symptom Score / Characteristic: Mean (SD) or n (%)	**Follow-up Cohort (n=252)**	**Deceased/ Too-Ill for Follow-up[b] (n=70)**	**Lost to Follow-up/ Withdrew[b] (n=38)**	**Alive at end of Follow-up (n=163)**	**Deceased during follow-up[c] (n=197)**	**No/Mild Cognitive Impairment (N=190)**	**Incident Cognitive Impairment[d] (N=34)**	**Cognitive Impairment at Baseline[d] (n=18)**
Age at Exam	68.8 (9.9)	76.41 (6.0) *	68.2 (13.4)	64.8 (10.4)	74.7 (7.4) *	68.0 (9.6)	71.3 (10.0)	73.2 (9.4) *
PD Duration at Exam, years	1.4 (1.7)	0.87 (1.5)	1.0 (1.3)	1.3 (1.6)	1.2 (1.7)	1.2 (1.4)	2.4 (1.7)	2.8 (2.6) *
PD Duration at Event/	--	--	--	12.1 (2.0)	7.1 (3.7) *	6.4 (2.1)	6.8 (2.3)	--
MMSE	28.1 (2.2)	26.4 (3.1) *	27.8 (2.6)	28.2 (2.3)	27.3 (2.7) *	28.7 (1.3)	27.9 (1.5) *	22.2 (2.6) *
GDS	3.2 (3.3)	4.4 (3.0) *	3.6 (2.8)	3.4 (3.6)	3.6 (2.9)	3.2 (3.4)	2.9 (2.9)	3.9 (2.9)
UPDRS III	19.6 (9.5)	27.8 (14.0) *	21.8 (10.7)	18.6 (8.9)	23.7 (12.2) *	18.9 (9.4)	21. 9 (8.5)	23.0 (11.8)
Resting tremor Score	1.7 (1.8)	3.0 (2.2)	1.7 (2.1)	1.6 (1.8)	1.9 (2.0)	1.7 (1.7)	1.4 (1.5)	2.3 (2.7)
Bradykinesia Score	6.6 (4.0)	9.9 (5.5) *	7.0 (4.1)	6.3 (3.9)	8.0 (4.8)	6.3 (3.8)	7.6 (4.3)	7.7 (4.5)
Rigidity Score	3.2 (2.4)	3.9 (3.0) *	3.8 (2.5)	3.0 (2.0)	3.7 (2.8) *	3.2 (2.4)	3.4 (2.4)	3.3 (1.9)
Postural Reflex Impairment Score	2.9 (2.0)	5.3 (3.3) *	3.2 (3.2)	2.6 (2.1)	4.2 (2.8) *	2.7 (1.9)	5.0 (2.0) *	3.4 (2.4)
PD Subtype, n (%)								
PIGD Dominant (≤1.0)	157 (65)	60 (86) *	27 (71) *	102 (63)	148 (75) *	119 (53)	26 (76) *	12 (67)
Indeterminate (1.01–1.5)	30 (12)	7 (10)	4 (11)	20 (12)	23 (12)	22 (12)	5 (15)	3 (17)
Tremor Dominant (>1.5)	55 (23)	3 (4)	7 (18)	41 (25)	26 (13)	49 (26)	3 (9)	3 (17)
Levodopa use, n (%) yes	157 (68)	57 (84) *	23 (61)	93 (60)	146 (78) *	119 (65)	27 (84) *	11 (65)
LD (mg/day)	287.5 (281.6)	323.9 (211.4)	250.7 (277.1)	257.4 (306.2)	313.3 (228.9) *	267.6 (282.3)	376.2 (245.9) *	333.2 (313.7)
LED (mg/day)	360.7 (289.2)	370.4 (243.6)	316.4 (297.4)	337.3 (319.1)	367.3 (245.3)	344.9 (291.7)	444.0 (251.3)	373 (316.4)

* p<0.05, based on chi-square or t-test. Abbreviations: MMSE=Mini-Mental State Exam; GDS=Geriatric Depression Scale; UPDRS=Unified Parkinson's Disease Rating Scale; PIGD=postural instability gait difficulty; LD=levodopa dose; LED=levodopa equivalent dose

[a] excludes10 participants who did not complete MMSE during follow-up, and 18 participants with cognitive impairment at baseline

[b] Compared with those with follow-up (whole cohort, n=252)

[c] Compared with those alive at end of follow-up; includes patients who died before follow-up exams

[d] Compared with No/Mild cognitive impairment group

J Parkinsons Dis. Author manuscript; available in PMC 2019 December 20.

Table 3.

Mean changes in symptom progression scores over follow-up by cognitive impairment and mortality.

Characteristic Mean (SD) or n (%)	No/Mild Cognitive Impairment (N=190)	Incident Cognitive Impairment (N=34)	P-value	Alive at end of Follow-up (n=136)	Deceased over Study Period (n=106)	P-value
Total MMSE Change	−0.63 (1.7)	−6.29 (4.1)	<.0001	−0.51 (3.1)	−2.07 (3.4)	0.0002
Average pt change/year	−0.11 (0.46)	−1.28 (0.87)	<.0001	−0.07 (0.06)	−0.51 (1.2)	0.0008
Total GDS Change	0.69 (3.0)	2.82 (3.6)	0.0004	0.32 (3.1)	1.84 (3.1)	0.0002
Average pt change/year	0.12 (0.80)	0.53 (0.68)	0.0062	0.03 (0.69)	0.39 (0.88)	0.0013
Depression (any GDS ≥ 7)	52 (27)	15 (44)	0.0495	47 (29)	53 (27)	0.6839
Total UPDRS Change	9.4 (11.6)	22.1 (17.8)	0.0010	9.4 (10.4)	13.8 (15.4)	0.0152
Average pt change/year	2.2 (2.6)	3.2 (2.9)	0.0367	1.97 (1.9)	2.96 (3.26)	0.0068
Fast motor progression[a]	21 (11)	11 (39)	0.0001	11 (8)	25 (25)	0.0007

Abbreviations: MMSE=Mini-Mental State Exam; GDS=Geriatric Depression Scale; UPDRS=Unified Parkinson's Disease Rating Scale

[a]We defined "fast" motor symptom decline as a 5 or more point increase in the annual rate of UPDRS-III change (Ritz, 2012)

Table 4.

Cox Proportional Hazards Ratio estimates for baseline characteristics and time to cognitive impairment and mortality

Baseline Characteristic	Time to Cognitive Impairment (n=224; 34 events)			Time to Mortality (n=360; 197 events)		
	HR* (95% CI)	p-value	FDR adj p-value	HR* (95% CI)	p-value	FDR adj p-value
Demographics						
Age at diagnosis	1.05 (1.01, 1.09)	0.0271	0.0759	1.09 (1.07, 1.11)	8.00E-20	4.40E-18
Sex	0.75 (0.35, 1.60)	0.4575	0.5342	1.01 (0.76, 1.36)	0.9271	0.9720
Non-European Ancestry	1.67 (0.69, 4.08)	0.2575	0.3697	1.19 (0.78, 1.81)	0.4148	0.5162
Education	0.89 (0.81, 0.99)	0.0255	0.0753	0.91 (0.85, 0.97)	0.0061	0.0286
Smoker	0.99 (0.47, 2.06)	0.9720	0.9720	1.41 (1.05, 1.90)	0.0209	0.0732
Pack-years	1.01 (0.99, 1.02)	0.5983	0.6838	1.01 (1.00, 1.01)	0.0005	0.0028
PD characteristics						
PD Duration	1.27 (1.02, 1.60)	0.0361	0.0859	1.07 (0.97, 1.18)	0.1604	0.2722
UPDRS III	1.03 (0.99, 1.08)	0.0925	0.1851	1.07 (1.05, 1.10)	1.41E-08	3.96E-07
Resting tremor Score	0.83 (0.63, 1.11)	0.2169	0.3374	1.13 (1.04, 1.22)	0.0047	0.0238
Bradykinesia Score	1.07 (0.97, 1.18)	0.1878	0.3092	1.20 (1.12, 1.28)	1.16E-07	1.63E-06
Rigidity Score	1.10 (0.94, 1.29)	0.2384	0.3534	1.14 (1.07, 1.20)	1.04E-05	9.70E-05
Postural Reflex Impairment Score	1.38 (1.16, 1.64)	0.0002	0.0020	1.29 (1.18, 1.41)	3.32E-08	6.20E-07
PD Subtype						
TD vs PIGD (ref)	0.21 (0.05, 0.91)	0.0368	0.0859	0.58 (0.38, 0.88)	0.0102	0.0440
TD vs IND (ref)	0.37 (0.06, 2.14)	0.2641	0.3697	0.57 (0.32, 1.00)	0.0517	0.1113
Levodopa Use, yes	3.23 (1.10, 9.48)	0.0335	0.0859	1.56 (1.09, 2.24)	0.0157	0.0588
LD (mg/day)	1.006 (0.997, 1.014)	0.1923	0.3105	1.005 (1.000, 1.010)	0.0569	0.1300
LED (mg/day)	1.006 (0.998, 1.015)	0.1454	0.2602	1.004 (0.999, 1.009)	0.0972	0.1877
MMSE	0.76 (0.60, 0.96)	0.0224	0.0737	0.79 (0.72, 0.87)	8.41E-07	9.42E-06
GDS	1.00 (0.88, 1.15)	0.9689	0.9720	1.18 (1.08, 1.29)	0.0002	0.0017
Health Indicators						
Self-reported (Has patient ever been told by a doctor, they have…)						
Diabetes	0.57 (0.17, 1.94)	0.3693	0.4810	1.35 (0.91, 1.98)	0.1340	0.2421
Stroke	1.76 (0.48, 6.41)	0.3914	0.4982	2.70 (1.23, 5.91)	0.0132	0.0529
Heart Attack	0.95 (0.22, 4.17)	0.947	0.9720	1.87 (1.23, 2.84)	0.0035	0.0198
High BP	0.68 (0.32, 1.42)	0.3054	0.4172	1.02 (0.76, 1.36)	0.9065	0.9720
Measured						
Systolic BP	0.99 (0.97, 1.01)	0.4579	0.5342	1.001 (0.995, 1.008)	0.6894	0.7722
Diastolic BP	1.01 (0.98, 1.05)	0.4373	0.5324	0.991 (0.981 (1.002)	0.1184	0.2211
BMI	1.01 (0.93, 1.09)	0.8295	0.9108	0.98 (0.95, 1.01)	0.2398	0.3534
Average Sleep Levels, per hr						
Lifetime	1.57 (1.02, 2.42)	0.0427	0.0956	1.08 (0.92, 1.28)	0.3279	0.4372
10 years prior to interview	1.34 (1.02, 1.77)	0.0363	0.0859	1.12 (1.02, 1.25)	0.0246	0.0753

*Models control for age at diagnosis, sex, European ancestry, education, and smoking

Abbreviations: UPDRS=Unified Parkinson's Disease Rating Scale; TD=tremor dominant; PIGD=postural instability gait difficulty; IND=indeterminate; LD=levodopa dose; LED=levodopa equivalent dose; MMSE=Mini-Mental State Exam; GDS=Geriatric Depression Scale; TBI=traumatic brain injury; BP=blood pressure; BMI=body mass index; FDR=False Discovery Rate