RESEARCH ARTICLE

The Emergence and Progression of Motor Dysfunction in Individuals at Risk of Parkinson's Disease

Cristina Simonet, MD, PhD,[1] Philipp Mahlknecht, MD, PhD,[2] Kathrin Marini, MD,[2] Klaus Seppi, MD,[2] Aneet Gill, BSc,[1] Jonathan P. Bestwick, MSc,[1] Andrew J. Lees, FRCP, PhD,[3] Gavin Giovannoni, FRCP, PhD,[1,4] Anette Schrag, FRCP, PhD,[3] and Alastair J. Noyce, FRCP, PhD[1*]

[1]*Preventive Neurology Unit, Wolfson Institute of Population Health, Queen Mary University of London, London, United Kingdom*
[2]*Department of Neurology, Innsbruck Medical University, Innsbruck, Austria*
[3]*Reta Lila Weston Institute of Neurological Studies, University College London Queen Square Institute of Neurology, London, United Kingdom*
[4]*Blizard Institute, Queen Mary University, London, United Kingdom*

ABSTRACT: Background: PREDICT-PD is a United Kingdom population-based study aiming to stratify individuals for future Parkinson's disease (PD) using a risk algorithm.

Methods: A randomly selected, representative sample of participants in PREDICT-PD were examined using several motor assessments, including the motor section of the Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS)-III, at baseline (2012) and after an average of 6 years of follow-up. We checked for new PD diagnoses in participants seen at baseline and examined the association between risk scores and incident sub-threshold parkinsonism, motor decline (increasing ≥5 points in MDS-UPDRS-III) and single motor domains in the MDS-UPDRS-III. We replicated analyses in two independent datasets (Bruneck and Parkinson's Progression Markers Initiative [PPMI]).

Results: After 6 years of follow-up, the PREDICT-PD higher-risk group (n = 33) had a greater motor decline compared with the lower-risk group (n = 95) (30% vs. 12.5%, $P = 0.031$). Two participants (both considered higher risk at baseline) were given a diagnosis of PD during follow-up, with motor signs emerging between 2 and 5 years before diagnosis. A meta-analysis of data from PREDICT-PD, Bruneck, and PPMI showed an association between PD risk estimates and incident sub-threshold parkinsonism (odds ratio [OR], 2.01 [95% confidence interval (CI), 1.55–2.61]), as well as new onset bradykinesia (OR, 1.69 [95% CI, 1.33–2.16]) and action tremor (OR, 1.61 [95% CI, 1.30–1.98]).

Conclusions: Risk estimates using the PREDICT-PD algorithm were associated with the occurrence of sub-threshold parkinsonism, including bradykinesia and action tremor. The algorithm could also identify individuals whose motor examination experience a decline over time. © 2023 The Authors. *Movement Disorders* published by Wiley Periodicals LLC on behalf of International Parkinson and Movement Disorder Society.

Key Words: Parkinson's disease; prediction; population-based cohort; motor progression

***Correspondence to:** Professor. Alastair J. Noyce, Preventive Neurology Unit, Wolfson Institute of Population Health, Queen Mary University of London, London, EC1M 6BQ, UK; E-mail: a.noyce@qmul.ac.uk

Relevant conflicts of interest/financial disclosures: C.S. was funded by Fundación Alfonso Martín Escudero while she carried out the current study.
Funding agencies: The PREDICT-PD study is funded by Parkinson's United Kingdom. The Preventive Neurology Unit is funded by the Barts Charity.

Received: 8 March 2023; **Revised:** 22 May 2023; **Accepted:** 24 May 2023

Published online in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/mds.29496

Introduction

Mild abnormalities in movement may be seen as part of normal aging and during the early stages of a number of neurodegenerative conditions, including Parkinson's disease (PD).[1,2] Different terms have been used to describe these signs including sub-threshold parkinsonism (SP), mild parkinsonian signs and soft or mild extrapyramidal signs. The progression of PD is gradual and slow. It is, therefore, probable that subtle motor manifestations appear years before clinical presentation or a diagnosis.[3] However, subtle non-progressive motor impairment in the elderly is not specific to PD and may be indicative of other neuropathology.[4]

PREDICT-PD is a cohort study, which aims to identify individuals at risk of future PD from the United Kingdom (UK) population.[5] After enrolment in the pilot phase of the study, individuals that were classified as being at higher risk (HR) or lower risk (LR) using an algorithm, were examined in person. Participants in the HR group were more likely to have subtle motor impairment compared with LR participants, defined as having higher scores in the motor part (III) of the Unified Parkinson's Disease Rating Scale (UPDRS) (median, 3; interquartile range [IQR], 1–5.5) than LR individuals (median, 1; IQR, 0–3; $P < 0.001$), and more likely to be classified as having SP.[6] A continuous relationship of risk estimates with the motor scores was observed (0.52-point increase in MDS-UPDRS-III per doubling of PD risk, 95% confidence interval [CI], 0.31–0.72; $P < 0.001$) after adjusting for confounders such as age, vascular risk factors, and cognitive test scores. Since then, the PREDICT-PD risk algorithm has been "enhanced" to include new determinants of risk, as well as modelling continuous data from objective olfactory and keyboard motor tasks.[4,7]

In this study, a follow-up of participants examined at baseline was carried out after ~6 years. The main aim of the present analysis was to show how aspects of motor dysfunction relate to the algorithm and progress over time.

Methods

The PREDICT-PD pilot cohort was established in 2011 with 1323 participants.[5] All volunteers were individuals over the age of 60 years, without known neurological disease, and resided in the UK. The exclusion criteria included a diagnosis of PD, other movement disorder, stroke, motor neuron disease, dementia, or treatment known to cause iatrogenic parkinsonism. Participants were recruited via an online media campaign (www.predictpd.com). A randomly selected sample of participants were seen in 2012 (baseline) and 2018 (follow-up). Here, we present a longitudinal study focused on clinical motor changes across this 6-year follow-up period (2012–2018) (Fig. 1).

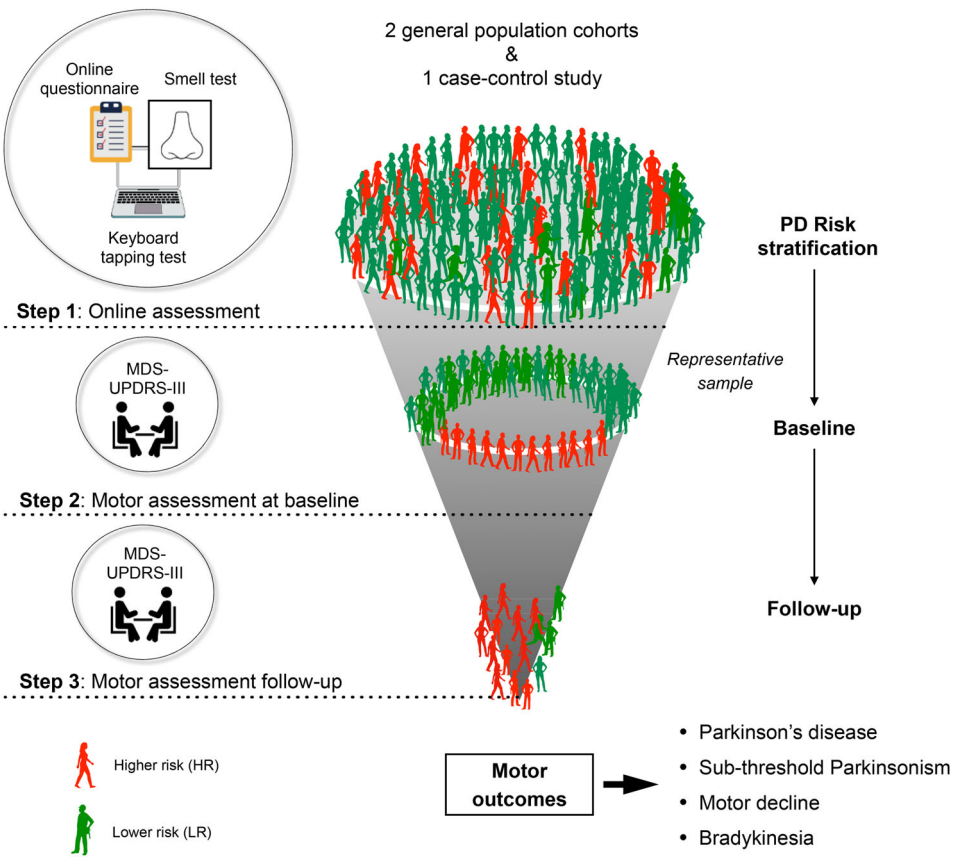

FIG. 1. Schematic of PREDICT-PD study. (1) Online population-based risk stratification. Stratification based on risk estimates: higher risk (red), lower risk (green). (2) In-person assessment of a representative group (n = 128). Motor outcomes: Parkinson's disease, Sub-threshold parkinsonism, motor decline (Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale [MDS-UPDRS-III] ≥5) and bradykinesia (bradykinesia MDS-UPDRS-III sub-score > 1).

We replicated some analyses in two additional datasets by classifying participants in a similar way to that of PREDICT-PD. The Bruneck study cohort is a prospective population-based study that has integrated evaluation for parkinsonism and PD risk factors in its protocol since 2005 in more than 500 subjects aged between 55 and 94 years old.[8] The Parkinson Progression Marker Initiative (PPMI) study is an observational, multi-center study designed to identify PD progression markers to improve understanding of disease etiology and course. The control group in PPMI are healthy people who have been followed over many years.[9]

Online Assessment

All PREDICT-PD participants were enrolled and assessed in the online study before being seen in person. The assessments included an evidence-based questionnaire derived from a systematic review,[10] followed by a validated keyboard tapping test,[11-13] and completion of a smell test.[7]

For the stratification of participants in the current study, we used the "enhanced" PREDICT-PD risk algorithm from the baseline year of assessment, which yields a greater range of risk estimates than the basic version (for more detailed information of the "enhanced" algorithm, see Supporting Data).[4,14] In brief, for each participant, the a priori age-related PD risk (expressed as an odds) was calculated and then adjusted depending on the presence and absence of determinants of risk, which included the following factors: sex, coffee use, current/former/never smoker, alcohol consumption, 1st degree relative with PD, constipation, erectile dysfunction, depression/anxiety, pesticides exposure, diabetes, head injury and non-steroidal anti-inflammatory drugs, calcium channel blockers, and beta blocker use. Regarding the intermediate clinical markers, continuous scores were used for BRadykinesia Akinesia INcoordination (BRAIN) test tapping speed and smell test scores. In contrast, rapid eye movement (REM) sleep behavior disorder (RBD) was used as a dichotomous variable (probable or not probable RBD) based on a pre-established cutoff (>5 points) extracted from RBD screening questionnaire (RBDSQ). More than 5 points in the RBDSQ has a sensitivity of 96% and specificity of 56% for video–polysomnography–confirmed isolated RBD.[15] People were classified in the HR and LR group based on risk estimates above or below the 15th centile, respectively. Of note, the 15th centile cutoff was calculated based on all risk scores from the wider PREDICT-PD cohort. We used the risk score at baseline to ensure that HR and LR at baseline and follow-up included the same individuals.

In-Person Assessment

Given that there were a small proportion of HR participants (defined as those above the 15th centile of risk estimate) in the original cohort, the selection process was done with preference for assessment of HR individuals. Lower risk subjects (and middle risk) were required for comparative analysis and also to maintain blinding of participants to risk. The selected sample of participants was seen in person at two time points (2012 and 2018). Participants were recorded on video at home and at both time points following the same instructions on the motor part (III) of MDS-UPDRS.[16] The same trained clinical rater (C.S.) scored both clinical examinations blinded to the risk scores, except for rigidity for which A.J.N. original scores were used. To ensure one assessment was not influencing the score of the other, videos recorded at baseline were scored 6 months after completing rating of all follow-up examinations. In addition to the MDS-UPDRS-III, the follow-up assessment (2018) included a timed handwriting task, which consisted of copying the sentence "Mary had a little lamb, its fleece was white as snow" three times using a pen and white paper.

Participants also completed the Montreal Cognitive Assessment (MoCA), which is a widely used screening instrument to detect cognitive impairment in PD.[17]

Motor Outcomes

New diagnoses of PD are the main outcome for the PREDICT-PD study. Considering the low incidence of PD, we here used three surrogate markers of PD at the follow-up examination to be used as binary outcomes for our prediction model: (1) development of SP (based on MDS research criteria for prodromal PD); (2) motor decline (≥5-point change in the MDS-UPDRS-III)[18] compared between four groups (based on the presence or absence of SP and being in the HR and LR group); and (3) abnormality of single motor domains from the MDS-UPDRS-III. A detailed definition of each outcome can be found in the Supporting Data.

Statistical Analysis

Data normality was assessed using the D'Agostino test. The mean and standard deviation (SD) were calculated for normally distributed data and median and IQR for non-normally distributed data. Quantitative data for motor outcomes were compared using the two-sample *t* test and Mann-Whitney *U* test, for normally and non-normally distributed data respectively. Categorical variables were presented by absolute frequency and percentage and compared using Fisher's exact test.

We applied three separate logistic regression models to assess the HR group for the occurrence of SP (outcome 1), motor decline (outcome 2), and separate

motor domains in the MDS-UPDRS-III (outcome 3), with the LR group as a reference. For each model, odds ratios (ORs) and 95% CIs were calculated.

For outcome 1 and 3, a replication analysis was performed using data from the PPMI study and Bruneck Study cohort using the 2005 assessment as baseline and the 2010 assessment as follow-up, as previously published.[19,20] For outcome 1, we excluded any motor marker from our algorithm at baseline as per the BRAIN test, in our cohort, and UPDRS-III in the Bruneck Study cohort and MDS-UPDRS-III in the PPMI study. For both outcomes (1 and 3), we used the logarithmic transformation of risk scores estimates as a continuous explanatory variable. For each logistic regression model with a continuous predictor (log-transformed risk scores), the Box-Tidwell test was performed to check for the assumption that the relationship between the logit and the predictor was linear. We meta-analyzed the data using fixed-effects model from the three studies to calculate a single pooled estimate with incident SP as an outcome.

We carried out a sensitivity analysis using linear regression models to analyze the relationship of continuous likelihood ratio estimates of PD with the MDS-UPDRS-III, which was the core motor test in the three motor outcomes. Logarithmic transformation of risk scores was undertaken to transform skewed data to approximately conform to a normal distribution. We used multivariate linear regression to examine the influence of potential confounding factors such as cognitive impairment (MoCA test scores), and vascular risk factors (hypertension, hypercholesterolemia, and history of ischemic heart disease). Type 2 diabetes (T2D) was not included as confounder because it is part of the enhanced PREDICT-PD algorithm. Although age can be expected to account for some motor score variation, it also has a strong weighting in the enhanced PREDICT-PD algorithm, rendering adjustment inappropriate. To avoid multicollinearity, we carried out another sensitivity analysis using a regression model without the contribution of age and sex to the likelihood ratios and then adjusting for age and sex.

All statistical tests were two-tailed. Because several analyses are presented, the significance level was set at <0.010. Data analysis was carried out using STATA v.13 (StataCorp, College Station, TX).

Results

Of 181 participants seen at baseline (HR, 48; LR, 133), two participants died, and 15 declined for personal and medical reasons. It was not possible to contact 32 participants. Thus, 132 participants (HR, 36; LR, 96) were reviewed in person. Four participants were subsequently excluded at follow-up in line with the exclusion criteria of the study (Fig. 2). Therefore, 128 participants (HR, 33; LR, 95) were included in the final analysis. Participants seen in person remained a representative sample of the entire cohort assessed online at baseline, which included participants not seen in person (Table S1 in the Supporting Data).

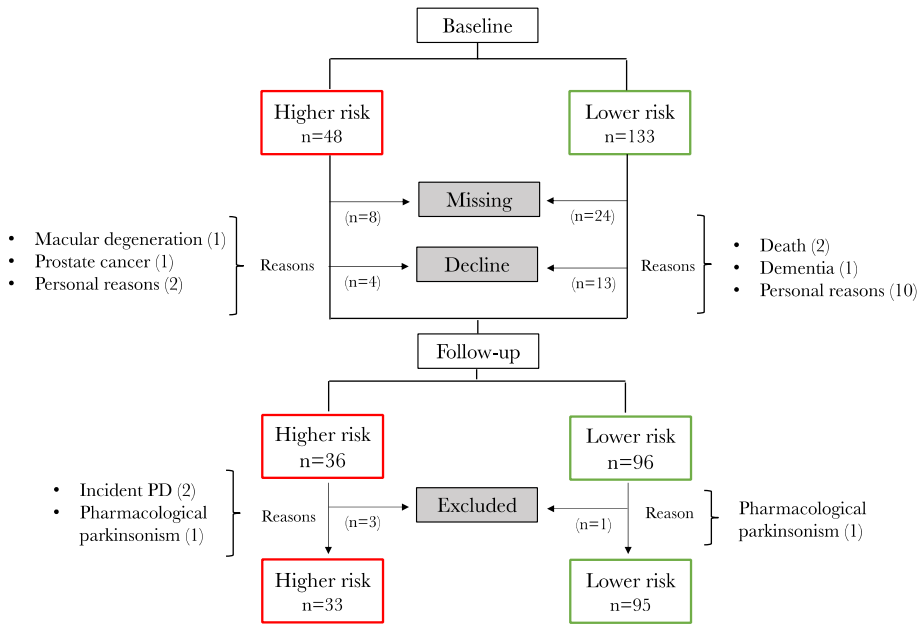

FIG. 2. Flow chart showing dropouts from the baseline study. Between brackets (number of participants). The higher and lower risk groups were classified using the enhanced risk algorithm at baseline. [Color figure can be viewed at wileyonlinelibrary.com]

The 33 HR participants seen in person were older ($P < 0.001$) and more likely to be male ($P = 0.001$) compared with the LR seen in person. Both groups had a similar proportion of vascular risk factors including T2D, hypertension, and high cholesterol (Table 1). The median MoCA score in the HR and LR groups was 27 and 28, and the sum of the ranks was lower in the HR group ($P < 0.001$).

Motor Progression

The median MDS-UPDRS-III score in the HR group was on average 3 and 4 points higher than in the LR group at baseline and follow-up, respectively. At follow-up, the HR group performed the handwriting test, on average, 10 seconds slower than LR participants (Table 1). Handwriting speed was not collected at baseline. Two participants from the baseline cohort were newly diagnosed with PD between 2012 and 2018. Of note, both were classified in the HR group at baseline and fulfilled criteria for SP at 2- and 5-year follow-up before receiving a formal PD diagnosis.

For each three logistic regression models the linearity assumption was satisfied (all $P > 0.05$, from Box-Tidwell test).

Outcome 1: Incident Sub-Threshold Parkinsonism

In PREDICT-PD, there was weak evidence that the HR group had a higher proportion of new cases of (incident) SP (6/33 (18.2%) vs. 7/33 (7.4%); $P = 0.096$) and that the odds of incident SP after 6 years were 1.7-fold greater per 1 unit change in the risk score (OR, 1.70; 95% CI, 0.99–2.94; coefficient, 0.53; intercept, 0.33; $P = 0.053$). Replication of this observation was carried out in the Bruneck and PPMI studies, using the same risk algorithm. In the Bruneck study, there was a clear association between risk scores and incident SP (OR 2.28; 95% CI, 1.55 –3.34; $P < 0.001$). A similar association was also observed in the PPMI study (OR, 1.90; 95% CI, 1.19–3.03; $P = 0.007$). Of note, there was a greater proportion of incident SP cases in the Bruneck cohort, compared with PREDICT-PD and PPMI (Bruneck 29.4%, PPMI 12.4%, PREDICT-PD

TABLE 1 *Demographic data, comorbidities and clinical manifestations in 2018*

	Higher risk (n = 33)	Lower risk (n = 95)	*P*-value
Age, mean (SD)	77.4 (4.6)	73.6 (5.0)	<0.001[a]
Male (%)	25 (75.8)	41 (43.2)	0.001
T2D, n (%)	8 (24.2)	10 (10.5)	0.078
Hypertension, n (%)	17 (51.5)	42 (44.2)	0.545
High cholesterol, n (%)	12 (36.4)	25 (26.3)	0.275
MoCA, median (IQR)	27 (25–28)	28 (26–9)	0.001[b]
Motor manifestations			
MDS-UPDRS-III, median (IQR) (2012)	5 (2–6)	2 (0–4)	<0.001[b]
MDS-UPDRS-III, median (IQR) (2018)	7 (3–9)	3 (1–5)	0.001[b]
Motor decline, n (%)	10 (30.3)	12 (12.6)	0.031
Motor improvement/stable, n (%)	23 (69.7)	83 (87.4)	0.001
Incident motor domains			
Bradykinesia, n (%)	19 (57.6)	27 (28.4)	0.003
Rigidity, n (%)	10 (30.3)	22 (23.2)	0.485
Rest tremor, n (%)	4 (12.1)	5 (5.3)	0.235
Action tremor, n (%)	25 (75.7)	44 (46.3)	0.004
Handwriting speed (sec), mean (SD)	71.91 (12.11)	61.23 (12.65)	<0.001[a]
BRAIN test-KS (taps/30 sec), mean (SD)	49.74 (11.37)	55.72 (12.41)	0.010[a]
Incident SP, n (%)	6 (18.2)	7 (7.4)	0.096

[a]All *P*-values from Fisher's exact test except for two-sample *t* test with equal variances; [b]Two-sample Wilcoxon rank-sum.
Abbreviations: SD, standard deviation; T2D, type 2 diabetes; MoCA, Montreal cognitive assessment; IQR, interquartile range; MDS-UPDRS-III items: bradykinesia (item 4–8 ≥ 2), rigidity (item 3 ≥ 2), rest tremor (item 17 ≥ 1), action tremor (item15, 16 ≥ 1); motor decline, ≥5-point MDS-UPDRS-III change, motor improvement/stable: <5-point change; MDS-UPDRS-III >6 (excluding action tremor); BRAIN, bradykinesia akinesia incoordination; KS, kinesia score; SP, sub-threshold parkinsonism.

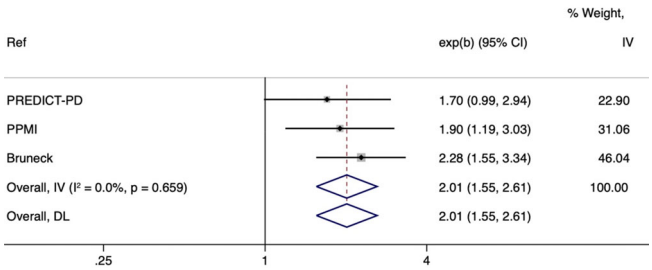

FIG. 3. Meta-analysis of the PREDICT-PD, Parkinson's Progression Markers Initiative (PPMI), and Bruneck studies. Mixed effect model using the odds ratio (exp(b) of developing incident sub-threshold parkinsonism [SP] in higher and lower risk groups. Three cohorts are not statistically significant heterogeneous ($P = 0.659$). [Color figure can be viewed at wileyonlinelibrary.com]

10.1%). A meta-analysis of the effect estimates from the three cohorts gave a combined OR of 2.01 (95% CI, 1.55–2.61; $P < 0.001$) (Fig. 3).

Outcome 2: Motor Decline

At baseline, the median MDS-UPDRS-III score in the HR group was 5 (IQR, 2–6) and 2 in the LR group (IQR, 0–4; $P < 0.001$). Six years later, people in the HR group still had higher motor scores than the LR group; the median MDS-UPDRS-III scores in the HR and LR groups were 7 and 3 (IQR, 3–9 and 1–5, respectively; $P = 0.001$). A greater proportion of people in the HR group (10/33 [30.3%]) had motor decline over time (≥5-point change in the motor scale) compared with the LR group (12/95 [12.6%]; $P = 0.031$) (Table 1). One hundred and six participants experienced either a motor score improvement or remained stable over time with <5-point change in the MDS-UPDRS-III (HR, 23 [69.7%]; LR, 83 [87.4%]; $P = 0.001$) with none of them having SP. There was nominal evidence that people in the HR group had 3-fold greater odds of experiencing motor decline (≥5-point change) than those in the LR (OR, 3.01; 95% CI, 1.15–7.84; coefficient, 1.10; intercept, −1.28; $P = 0.024$).

Outcome 3: New Abnormalities in Single Motor Domains

New onset (incident) bradykinesia was more common in the HR group than in the LR group 19 (57.6% vs 28.4%; $P = 0.003$). Similarly, people classified in the HR were more likely to have new onset action tremor (75.7% vs. 46.3%; $P = 0.004$). Table 1 gives a summary of the proportion of individual motor signs in the HR and LR groups. In a logistic regression model using incident bradykinesia as the motor outcome, there was nominal evidence that HR people had more than twice the odds of developing bradykinesia over time (OR, 2.67; 95% CI, 1.07–, 6.62; coefficient, 0.98; intercept, −1.67; $P = 0.035$). The association between incident bradykinesia and HR of PD became stronger after adjusting for age and sex (adjusted OR, 5.88; 95% CI, 1.83–18.92; coefficient, 1.78; intercept, 7.49; $P = 0.011$). People at HR were three times more likely to have a new onset action tremor (OR, 3.60; 95% CI, 1.60–8.21; coefficient, 1.28, intercept 0.98; $P = 0.002$). In contrast with bradykinesia, the association between being HR and incident action tremor weakened after adjusting for age and sex (adjusted OR, 2.40; 95% CI, 0.95–6.37; coefficient, 0.88; intercept, 6.44; $P = 0.063$), suggesting a confounding effect. Participants with action tremor (n = 69) were older

TABLE 2 *Linear regression analysis between baseline risk estimates and follow-up MDS-UPDRS-III scores*

Baseline risk score	Increase in MDS-UPDRS-III per doubling of odds (β)	95% CI	*P* value
Crude	1.66	1.04 – 2.27	<0.001
Adjusted for MoCA	1.82	1.19 – 2.45	<0.001
Adjusted for VRF	1.38	0.77 – 1.99	<0.001
Adjusted for MoCA and VRF	1.56	0.94 – 2.17	<0.001
Baseline risk score (excluding age and sex)	**Increase in MDS-UPDRS-III per doubling of odds (β)**	**95% CI**	***P* value**
Crude	1.73	1.08 – 2.39	<0.001
Adjusted for MoCa	1.88	1.21 – 2.56	<0.001
Adjusted for VRF	1.44	0.80 – 2.09	<0.001
Adjusted for all co-variates	1.48	0.78 – 2.18	<0.001

Note: Simple (crude) and multivariate (adjusted) regression model for the association between baseline risk estimates (independent variable) and follow-up MDS-UPDRS-III scores (dependent variable).
Abbreviations: MDS-UPDRS-III, Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale motor examination; CI, confidence interval; MoCA: Montreal Cognitive Assessment; VRF, vascular risk factors (hypertension and high cholesterol).

(75.8 years [SD, 5.3] vs. 73.2 [SD, 4.7]; $P = 0.002$) and more likely to be male (63.8% vs. 41.7%, $P = 0.004$) than those without action tremor and have vascular risk factors (68.1% vs. 31.9%; $P = 0.002$) compared with those without action tremor. An association between being HR and having rigidity or rest tremor could not be demonstrated.

When using risk scores as a continuous variable, incident bradykinesia and action tremor also showed a positive association. The odds of having new onset bradykinesia after 6 years was 1.6-fold greater per 1 unit change in the risk score (95% CI, 1.14–2.20; $P = 0.005$). A replication of this analysis was carried out in the Bruneck and PPMI studies. The meta-analysis of the three studies had a pooled OR, 1.69 (95% CI, 1.33–2.16; $P < 0.001$). Like bradykinesia, new occurrence of action tremor showed an association with risk scores when pooling data from the three cohort studies (OR, 1.61; 95% CI, 1.30–1.98) (Supplementary Table S2).

Sensitivity Analysis

Risk scores at baseline were associated with higher motor scores at follow-up. Per doubling of risk at baseline, the MDS-UPDRS-III at follow-up increased 1.66 points (95% CI, 1.04–2.27; $P < 0.001$) (Table 2). Excluding tapping speed scores from the algorithm did not make any difference, suggesting that the BRAIN test might not have an important role in the algorithm in this subgroup analysis. Adjusting the regression models for MoCA scores did not show any major change in the effect estimates. In contrast, the regression coefficient from regression models changed to a greater extent after adjusting for vascular risk factors, which suggests a possible confounding role. A similar trend was seen when adjusting for vascular risk factors after having excluded age and sex from the algorithm (unadjusted β, 1.73; 95% CI, 1.08–2.39; adjusted β, 1.44; 95% CI, 0.80–2.09), suggesting that the confounding role of vascular risk factors was not explained by age or sex. Although there was some evidence of age and sex influencing risk estimates and motor score (unadjusted β, 1.73; 95% CI, 1.08–2.39; adjusted β, 1.58; 95% CI, 0.88–2.29), the discrepancies between unadjusted and adjusted regression models were not big enough for them to be considered confounding factors (Table 2).

Discussion

In the current manuscript, we investigated the course of motor prodromes in individuals stratified for future risk of PD. In a previous study, we reported that higher risk individuals, using the basic PREDICT-PD algorithm, exhibited an increased severity of motor disturbances and a greater proportion fulfilled clinical criteria for SP in a cross-sectional analysis.[6]

Merging data from three separate longitudinal studies (PREDICT-PD, Bruneck, and PPMI), showed that higher risk individuals (stratified using the "enhanced" PREDICT-PD risk algorithm) were more likely to develop new onset SP over time, with a doubling of SP at follow-up per 1 unit change in the risk score. We used SP as an outcome instead of incident PD because of the limited number of new onset PD cases, which is a common limitation in population-based studies. In fact, the MDS research criteria for prodromal PD show a low sensitivity in predicting incident PD-validation studies from four separate population-based cohorts (HELIAD, TREND PRIPS, and Bruneck studies)[21,22,23] showed that although MDS prodromal PD score had a high specificity (>80%), it had a limited sensitivity (4.5%–66.7%). Taking altogether, we might need to consider using intermediate motor outcomes to improve enrichment in population-based studies.

In this present study, having SP at baseline was associated with a larger motor decline over time. The definition of SP used was based on the MDS-UPDRS-III scores, which was also found to be associated with baseline PREDICT-PD risk score. However, the MDS-UPDRS-III was not designed to assess people without PD and the disproportionate representation of rest tremor (33% of the total MDS-UPDRS-III items) and scoring of other motor signs that are not commonly present at early stage (eg, freezing, postural instability) might have diluted the association between risk estimates and motor impairment. To overcome this limitation, we focused on each motor domain in the MDS-UPDRS-III separately and found an association between incident bradykinesia and being classified in the HR group at baseline. Moreover, slow handwriting, which could be considered a surrogate maker of bradykinesia, was more common in HR people than the LR group.[24] The definition of bradykinesia still relies on a scale that has not been designed for early stages of PD.[25] There is a need to validate adapted tools to detect the earliest deficits that later give rise to "true bradykinesia". In contrast with bradykinesia, the association of action tremor and abnormal gait with HR appeared to be influenced by age and sex in our cohort. This is in line with what has been classically described about bradykinesia being a genuine sign of PD from the early stages of the disease, in contrast to abnormal gait and action tremor, which are commonly present in elderly people without PD.[26,27]

Motor dysfunction is not exclusive to PD and may occur in healthy elderly people. The prevalence of SP in population-based studies ranges from 30% to 40% in this population, which is much higher than the prevalence of PD.[28] In one study based on a community setting, SP was found in more than one third of

individuals over the age of 65 years.[29] In another study carried out by Minn Aye and collaborators,[30] they found that one quarter of their cohort exhibited SP, with three of 10 people older than 75 showing some degree of motor dysfunction. After adjusting for age and sex, cognitive dysfunction together with symptoms of RBD, were found to be related to SP, suggesting that an underlying neurodegenerative process might be present in a proportion of them. In line with these findings, the relationship between PREDICT-PD risk estimates and MDS-UPDRS-III did not differ much after removing age and sex from our algorithm. That suggests motor dysfunction could be related to the combination of multiple risk factors other than age and sex.

Apart from future risk of PD, SP has also been found to be associated with future dementia, particularly in the elderly population[2] and with cerebrovascular disease.[26] We adjusted for both factors in our analysis. Unlike MoCA scores, the strength of association decreased significantly after adjusting for vascular risk factors. This pattern was maintained even after removing age and sex from the algorithm, suggesting that their confounding effect was not driven by age or sex. The contribution of cerebrovascular disease to the presence of mild parkinsonian signs has been studied in the ageing population. In one clinic-pathological study, in which 418 brain autopsies had been evaluated for parkinsonism during life,[31] people with macroscopic infarcts were more likely to have had higher global parkinsonian scores. This study, together with our findings, supports the idea of vascular risk factors as a risk for PD.

There are several limitations to this study. First, two consecutive assessments with 6 years in between makes establishing accurate motor trends difficult. Motor changes could be influenced by other external factors, such as low mood or concomitant medication. We took these possibilities into account and tried to minimize the interference of external factors generally by examining participants in the same environment (home). We also specifically checked for concurrent medication and diagnosed depression. With the intention of trying to mitigate observational bias, we scored videos at baseline instead of using the scores extracted in person by A.J.N. By doing this we ascertained important information that can only be appreciated in person, such as subtle tremor, and might be missed in the video. A proportion of participants were missing (17% of the baseline cohort) and a further 9% dropped out of the study. The possibility of some of them having received the diagnosis of PD after baseline assessment cannot be ruled out. In fact, apart from motivational aspects, symptom perception could make participants more anxious and therefore, drop out of the study.[32] Therefore, it could be expected that among those people who drop out of the study, there were a few unreported incident PD cases. This in turn might have underestimated or overestimated the prediction power of our algorithm. The lack of incident PD cases limited the scope of the statistical analysis, meaning that survival analysis was not possible to be calculated to extract the prediction power of motor prodromes. Finally, in the present study we dichotomized a continuous variable (PREDICT-PD risk score) based on an arbitrary cutoff (15th centile) without accounting for the "dose effect" of risk estimates. Those participants at middle risk were included in the LR group, making the LR a more heterogeneous group in terms of risk score ranges. Therefore, it is expected that some participants close to the 15th centile were classified in the LR group (false negative), leading to some ascertainment bias. We used the same sampling approach to baseline study to maintain methodological consistency across the studies. However, the fact that we undertook two replication studies to analyze the relationship between continuous risk score (unstratified) data and motor outcomes is a strength of the present study.

The PREDICT-PD approach is a low intensity and cost-efficient assessment, which makes it a feasible method for larger scale studies. Our algorithm seems to be able to estimate the occurrence of motor disturbances in the future, in particular SP and bradykinesia. Adding new incident PD cases will help to understand, which pre-diagnostic features best predict future diagnosis of PD.

Acknowledgment: All participants of the study.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

References

1. Mahlknecht P, Seppi K, Poewe W. The concept of prodromal Parkinson's disease. J Parkinsons Dis 2015;5:681–697.
2. Buchanan SM, Richards M, Schott JM, Schrag A. Mild Parkinsonian signs: a systematic review of clinical, imaging, and pathological associations. Mov Disord 2021;36:2481–2493.
3. Gibb WRG, Lees AJ. The relevance of the Lewy body to the pathogenesis of idiopathic Parkinson's disease. J Neurol Neurosurg Psychiatry 1988;51:745–752.
4. 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 Parkinson's Dis 2021;7:1–7.
5. Noyce AJ, Bestwick JP, Silveira-Moriyama L, Hawkes CH, Knowles CH, Hardy J, et al. PREDICT-PD: identifying risk of Parkinson's disease in the community: methods and baseline results. J Neurol Neurosurg Psychiatry 2014;85:31–37.
6. Noyce AJ, Schrag A, Masters JM, Bestwick JP, Giovannoni G, Lees AJ. Subtle motor disturbances in PREDICT-PD participants. J Neurol Neurosurg Psychiatry 2017;88:212–217.
7. Bestwick JP, Auger SD, Schrag AE, Grosset DG, Kanavou S, Giovannoni G, et al. Optimising classification of Parkinson's disease

based on motor, olfactory, neuropsychiatric and sleep features. npj Parkinson's Dis 2021;7:87.

8. Mahlknecht P, Seppi K, Stockner H, Nocker M, Scherfler C, Kiechl S, et al. Substantia Nigra hyperechogenicity as a marker for Parkinson's disease: a population-based study. Neurodegener Dis 2013;12:212–218.
9. Marek K, Jennings D, Lasch S, Siderowf A, Tanner C, Simuni T, et al. The Parkinson progression marker initiative (PPMI). Prog Neurobiol 2011;95:629–635.
10. Noyce AJ, Bestwick JP, Silveira-Moriyama L, Hawkes CH, Giovannoni G, Lees AJ, et al. Meta-analysis of early nonmotor features and risk factors for Parkinson disease. Ann Neurol 2012;72: 893–901.
11. Noyce AJ, Nagy A, Acharya S, Hadavi S, Bestwick JP, Fearnley J, et al. Bradykinesia-Akinesia incoordination test: validating an online keyboard test of upper limb function. PLoS One 2014;9:e96260.
12. Shribman S, Hasan H, Hadavi S, Giovannoni G, Noyce AJ. The BRAIN test: a keyboard-tapping test to assess disability and clinical features of multiple sclerosis. J Neurol 2018;265:285–290.
13. Hasan H, Burrows M, Athauda DS, Hellman B, James B, Warner T, et al. The BRadykinesia akinesia in coordination (BRAIN) tap test: capturing the sequence effect. Mov Disord Clin Pract 2019;6: 462–469.
14. Bestwick JP, Auger SD, Schrag AE, Grosset DD, Kanavou S, Giovannoni G, et al. Maximising information on smell, quantitative motor impairment and probable REM-sleep behaviour disorder in the prediction of Parkinson's disease. medRxiv 2020:2020–03.
15. Stiasny-Kolster K, Mayer G, Schäfer S, Möller JC, Heinzel-Gutenbrunner M, Oertel WH. The REM sleep behavior disorder screening questionnaire—a new diagnostic instrument. Mov Disord 2007;22:2386–2393.
16. Goetz CG, Fahn S, Martinez-Martin P, Poewe W, Sampaio C, Stebbins GT, et al. Movement disorder society-sponsored revision of the unified Parkinson's disease rating scale (MDS-UPDRS): process, format, and clinimetric testing plan. Mov Disord 2007;22:41–47.
17. Dalrymple-Alford JC, MacAskill MR, Nakas CT, Livingston L, Graham C, Crucian GP, et al. The MoCA. Neurology 2010;75: 1717–1725.
18. Shulman LM, Gruber-Baldini AL, Anderson KE, Fishman PS, Reich SG, Weiner WJ. The clinically important difference on the unified Parkinson's disease rating scale. Arch Neurol 2010;67: 64–70.
19. Mahlknecht P, Kiechl S, Stockner H, Willeit J, Gasperi A, Poewe W, et al. Predictors for mild Parkinsonian signs: a prospective population-based study. Parkinsonism Relat Disord 2015;21: 321–324.
20. Marini K, Mahlknecht P, Tutzer F, Stockner H, Gasperi A, Djamshidian A, et al. Application of a simple Parkinson's disease risk score in a longitudinal population-based cohort. Mov Disord 2020;35:1658–1662.
21. Giagkou N, Maraki MI, Yannakoulia M, Kosmidis MH, Dardiotis E, Hadjigeorgiou GM, et al. A prospective validation of the updated movement disorders society research criteria for prodromal Parkinson's disease. Mov Disord 2020;35:1802–1809.
22. Pilotto A, Heinzel S, Suenkel U, Lerche S, Brockmann K, Roeben B, et al. Application of the movement disorder society prodromal Parkinson's disease research criteria in 2 independent prospective cohorts. Mov Disord 2017;32:1025–1034.
23. Mahlknecht P, Gasperi A, Djamshidian A, Kiechl S, Stockner H, Willeit P, et al. Performance of the movement disorders society criteria for prodromal Parkinson's disease: a population-based 10-year study. Mov Disord 2018;33:405–413.
24. Simonet C, Schrag A, Lees AJJ, Noyce AJJ. The motor prodromes of Parkinson's disease: from bedside observation to large-scale application. J Neurol 2019;268:2099–2108.
25. Heldman DA, Giuffrida JP, Chen R, Payne M, Mazzella F, Duker AP, et al. The modified bradykinesia rating scale for Parkinson's disease: reliability and comparison with kinematic measures. Mov Disord 2011;26:1859–1863.
26. Louis ED, Bennett DA. Mild Parkinsonian signs: an overview of an emerging concept. Mov Disord 2007;22:1681–1688.
27. Berg D, Marek K, Ross GW, Poewe W. Defining at-risk populations for Parkinson's disease: lessons from ongoing studies. Mov Disord 2012;27:656–665.
28. Louis ED, Luchsinger JA, Tang MX, Mayeux R. Parkinsonian signs in older people: prevalence and associations with smoking and coffee. Neurology 2003;61:24–28.
29. Bennett DA, Beckett LA, Murray AM, Shannon KM, Goetz CG, Pilgrim DM, et al. Prevalence of Parkinsonian signs and associated mortality in a community population of older people. N Engl J Med 1996;334:71–76.
30. Aye YM, Liew GM, Ng SYE, Wen M-C, Lim LLH, Chua S-T, et al. Mild Parkinsonian signs in a community ambulant population. J Parkinsons Dis 2020;10:1231–1237.
31. Buchman AS, Leurgans SE, Nag S, Bennett DA, Schneider JA. Cerebrovascular disease pathology and Parkinsonian signs in old age. Stroke 2011;42:3183–3189.
32. Lacey RJ, Jordan KP, Croft PR. Does attrition during follow-up of a population cohort study inevitably lead to biased estimates of health status? PLoS One 2013;8:e83948.

Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher's web-site.

SGML and CITI Use Only
DO NOT PRINT

Author Roles

(1) Research project: A. Conception, B. Organization, C. Execution; (2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique; (3) Manuscript Preparation: A. Writing of the First Draft, B. Review and Critique.

C.S.: 1A, 1B, 1C. 2A, 2B, 2C. 3A, 3B.
P.M.: 1C. 2A, 2B, 2C. 3B.
K.M.: 1C. 2A, 2B, 2C. 3B.
K.S.: 2C, 3B.
A.G.: 2C, 3B.
J.P.B.: 2C, 3B.
A.J.L.: 2C, 3B.
G.G.: 2C, 3B.
A.S.: 2C, 3B.
A.J.N.: 1A, 1B, 2C, 3B.

Financial Disclosures (For the Preceding 12 Months)

K.S. reports personal fees from Teva, UCB, Lundbeck, AOP Orphan Pharmaceuticals AG, Roche, Grünenthal, Stada, Licher Pharma, Biogen, BIAL, and AbbVie; honoraria from the IPMDS; research grants from FWF Austrian Science Fund, The Michael J. Fox Foundation, and AOP Orphan Pharmaceuticals AG, outside the submitted work. G.G. reports having received compensation for serving as a consultant or speaker for or having received research support from AbbVie, Aslan, Atara Bio, Biogen, BMS-Celgene, GlaxoSmithKline, Janssens/JandJ, Japanese Tobacco, Jazz Pharmaceuticals, LifNano, Merck and Co, Merck KGaA/EMD Serono, Moderna, Novartis, Sanofi and Roche/Genentech. A.S. reports having received research funding or support in the last 12 months from University College London, National Institute of Health (NIHR), National Institute for Health Research ULCH Biomedical Research Centre, the International Parkinson and Movement Disorder Society (IPMDS), the European Commission, Parkinson's UK and the Economic and Social Research Council. Honoraria for consultancy from Abbvie; and license fee payments from the University College London. Royalties from Oxford University Press. A.J.N. reports grants from Parkinson's UK, Barts Charity, Cure Parkinson's, National Institute for Health and Care Research, Innovate UK, Virginia Keiley benefaction, Solvemed, the Medical College of Saint Bartholomew's Hospital Trust, Alchemab, Aligning Science Across Parkinson's Global Parkinson's Genetics Program (ASAP-GP2) and The Michael J. Fox Foundation. Prof Noyce reports consultancy and personal fees from AstraZeneca, AbbVie, Profile, Roche, Biogen, UCB, Bial, Charco Neurotech, uMedeor, Alchemab, Sosei Heptares and Britannia, outside the submitted work. The rest of the co-authors do not have funding sources to report in the previous 12 months.