# Motor complications in Parkinson's disease: results from 3,343 patients followed for up to 12 years

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Word count (abstract): 249 words

Word count (main text): 3928 words

**Running title**: Motor complications in Parkinson's disease

**Key words:** Parkinson's, motor complications, dyskinesia, dystonia

**Motor complications in Parkinson's disease: results from 3,343 patients followed for up to 12 years**

**Background:** Motor complications are well recognised in Parkinson's disease (PD), but their reported prevalence varies and functional impact has not been well studied.

**Objectives:** To quantify the presence, severity, impact and associated factors for motor complications in PD.

**Methods:** Analysis of 3 large prospective cohort studies of recent-onset PD patients followed for up to 12 years. The MDS-UPDRS part 4 assessed motor complications and multivariable logistic regression tested for associations. Genetic risk score (GRS) for Parkinson's was calculated from 79 single nucleotide polymorphisms.

**Results:** 3,343 cases were included (64.7% male). Off periods affected 35.0% (95% CI 33.0, 37.0) at 4-6 years and 59.0% (55.6, 62.3) at 8-10 years. Dyskinesia affected 18.5% (95% CI 16.9, 20.2) at 4-6 years and 42.1% (38.7, 45.5) at 8-10 years. Dystonia affected 13.4% (12.1, 14.9) at 4-6 years and 22.8% (20.1, 25.9) at 8-10 years. Off periods consistently caused greater functional impact than dyskinesia. Motor complications were more common among those with higher drug doses, younger age at diagnosis, female gender, and greater dopaminergic responsiveness (in challenge tests), with associations emerging 2 to 4 years post-diagnosis. Higher Parkinson's GRS was associated with early dyskinesia ($0.026 \leq P \leq 0.050$ from 2 to 6 years).

**Conclusions:** Off periods are more common and cause greater functional impairment than dyskinesia. We confirm previously reported associations between motor

complications with several demographic and medication factors. Greater dopaminergic responsiveness and a higher genetic risk score are two novel and significant independent risk factors for the development of motor complications.

Motor complications are common in Parkinson's disease (PD), but their reported prevalence varies. Early studies reported more dyskinesia (49-88% after 5 years) than wearing off (41-80% after 5 years) as reviewed by Nutt[1]. More recent studies found dyskinesia and off periods to be less common, probably due to the lower L-dopa doses prescribed[2]. A range of 21 to 54% for off periods and 15 to 28% for dyskinesia has been reported previously at 4 to 6 years of disease[3-6]. In the largest recent study, off periods affected 34.7% while dyskinesia affected 25.3% of 734 patients followed for up to 10 years[7]. In most of the recent studies, the higher prevalence of dyskinesia over off periods seen in earlier studies has therefore been reversed. However, the functional impact of motor complications is much less well studied than their prevalence. This is important since a large proportion of dyskinesia is non-troublesome to patients[8]. Dystonia has not been assessed in previous major studies evaluating motor complications[3-5, 7, 9] and its predictive factors are therefore not yet defined.

The present study uses data from three large prospective cohorts to examine the prevalence of motor complications, evaluate their functional impact and describe their associated demographic and clinical factors over the natural history of PD. We define these features as seen in the current clinical management of PD, updating and extending the size and scope of previous work[7], as well as increasing the precision of previous prevalence estimates. In addition to the known range of risk factors for motor complications[5, 7, 9-13], we have analyzed detailed data on dopa responsiveness as well as the PD genetic risk score (GRS) and the rate of change in motor severity.

## Methods

3,453 patients were recruited between 2010 and 2014 to one of three cohort studies: the *Tracking Parkinson's* (n = 1,987) and *Oxford Discovery* (n = 1,043) studies in the UK; and the *Parkinson's Progression Markers Initiative (PPMI)* study in the United States (US), Europe, UK, and Australia (n = 423). Patients were recruited up to 3.5 years after diagnosis in the *Tracking Parkinson's* and *Oxford Discovery* studies, and up to 2 years after diagnosis in *PPMI.* 110 patients (*Tracking Parkinson's* 34; *Oxford Discovery* 70; *PPMI* 6), 3.2%, were excluded from further analysis due to a subsequent change in diagnosis. 3,343 patients were therefore included in the analysis (*Tracking Parkinson's* n = 1,953; *Oxford Discovery* n = 973; *PPMI* n = 417). Cases were prospectively followed for a maximum of 12 years. Comprehensive clinician and patient scoring assessments were performed in each cohort[14-16]. For the present study, the disease duration since diagnosis was divided into successive 2-year time bands, and clinical observations made closest to the midpoint of each time band were collated from the three cohorts. If participants were recruited between 2 to 4 years disease rather than 0 to 2 years, their baseline assessments were included in the 2 to 4 year time interval. Heterogeneity between the three cohorts was checked for by visual inspection.

The MDS-UPDRS part 4 grades both the time spent with dyskinesia and motor fluctuations, and the resulting functional impact. The complexity of motor fluctuations describes their predictability. For dystonia the proportion of time spent with painful dystonia out of the total time in an off state is rated[17].

The motor response (%) to a standard morning dose of L-dopa in patients prescribed L-dopa (*Tracking* and *Discovery*), or to a standard morning dose of a dopamine agonist and/or L-dopa (*PPMI*) was calculated from MDS-UPDRS part 3 scores at around three years after diagnosis. Dopaminergic therapy was omitted for at least 6 hours for standard-release preparations (or 12 hours for sustained-release preparations), and dopaminergic responsiveness was determined by the following formula: (off-score – on-score)/off-score x 100.

Covariates of interest were identified and selected based upon previous studies[5, 7, 9-13] and included: age at diagnosis, sex/gender, body mass index (BMI), education exceeding 12 years, the presence of depression and / or anxiety, MDS-UPDRS part 1 – 3 scores, including the tremor subscore, motor progression over time on the MDS-UPDRS part 3, cognition based on the Montreal Cognitive Assessment (MoCA) adjusted for education, Hoehn and Yahr disease severity, total levodopa equivalent daily dose (LEDD), the Parkinson's GRS, and dopaminergic responsiveness. Depression and anxiety were defined by a score > 1 on questions 1.3 and 1.4 on part 1 of the MDS-UPDRS, respectively. All covariates were assessed at baseline and during each consecutive 2-year time interval over the 12 years of follow-up.

If education values were missing, unadjusted MoCA scores were used as a modal (or median) imputation as most cases without missing education values had attained higher education. Missing items in the MDS-UPDRS parts 1, 2 and 3 were imputed using the average score of the available items for each scale at each visit. For MDS-UPDRS parts 1, 2 and the tremor subscore of the MDS-UPDRS part 3, imputation has been performed only if a single item was missing. For the MDS-UPDRS part 3,

imputation was performed for up to three missing items[18]. If more items were missing, no total scores were derived. Missing values for BMI were imputed by temporal linear interpolation if both an earlier and a later score were available for a subject, or else by carrying the last observation forward or first observation backward. Motor progression was estimated as the random slopes of a longitudinal multilevel model with random slope and intercept model for the MDS-UPDRS 3 total scores.

A genetic risk score for Parkinson's was calculated using 90 genome wide significant "hits" ($p < 5x10e-8$) from a large genome wide association study[19]. We obtained the beta coefficients from this study and multiplied them by the corresponding number of effect alleles for single-nucleotide polymorphisms (SNPs) in our three cohorts. Palindromic SNPs with minor-allele frequencies > 0.45 were excluded. This GRS provides an estimate of the contribution of genetics to developing PD[20]. To ensure consistency of the GRS across the cohorts, only the 79 relevant SNPs which were available (and non-palindromic) for all three cohorts were used.

To identify associations between the prevalence of motor complications and the covariates of interest, uni- and multivariable logistic regression was performed. Model coefficients were estimated separately and independently for each two-year interval, taking into account that associations may vary over time. The 0-2 year interval was excluded as motor complications were too rare to estimate reliable coefficients. Univariable models were fitted for each covariate of interest. Covariates with $P < 0.1$ in the univariable analyses for at least two time intervals were included in the multivariable models for the respective motor complication. Multivariable

models were fitted on complete cases, i.e., all cases with no missing data for outcome or any of the model covariates after imputation. Lasso logistic regression was performed as a sensitivity analysis using the R package glmnet[21] with an internal 10-fold cross validation to obtain a suitable penalty term (lambda) for each model. Cases were allocated to one of five quintiles (q1 low to q5 high) based upon the probability of each motor complication as estimated by lasso regression model.

Dopaminergic responsiveness was excluded from the primary multivariable models outlined above, as challenge tests were performed in only 54.6% of the subjects included in this analysis (*Tracking Parkinson's* 1229 out of 1953; *Oxford Discovery* 283 out of 973; *PPMI* 313 out of 417; Total: 1825 out of 3343). Associations between dopaminergic responsiveness and motor complications were studied by fitting secondary bivariable logistic models using the observed motor complication as the outcome with dopaminergic responsiveness and predicted log odds of each respective motor complication as estimated from the primary multivariable model as explanatory covariates.

To test if associations between motor complications and our covariates of interest differ between male and female or younger and older subjects, supplementary multivariable models including first-order interaction terms were fitted. These models were fitted using an identical set of covariates as the corresponding primary multivariable models plus one first-order interaction term each. Interactions between age at diagnosis and all other covariates (e.g., LEDD x age at diagnosis) as well as gender and all other covariates (e.g., LEDD x gender) have been explored.

Data preparation was carried out in STATA[22]. Statistical analysis and modeling has been conducted in R[23].

## Results

Of the 3,343 patients, 64.7% were male and the mean age at diagnosis across the 3 cohorts was 65.6 years (SD 9.6 years). 19.9% of patients were drug-naïve at 0-2 years and 4.5% at 2-4 years. The demographic and clinical variables are detailed in Table 1.

Tests for heterogeneity revealed some minor discrepancies in the demographic and clinical features between the three cohorts, but they were broadly homogenous (Supplementary Figures 1-4). In comparison to the *Tracking Parkinson's* and *Oxford Discovery* cohorts, PPMI cases were generally younger, with higher MoCA scores, less progression on the MDS-UPDRS part 3, and more frequent use of amantadine (Supplementary Figures 2, 3 and 4). The *Tracking Parkinson's* cohort had higher rates of anxiety and depression, and a greater proportion of cases with a Hoehn and Yahr score of 3 (Supplementary Figure 4).

*Motor complications*

Off periods were the most frequent complication followed by dyskinesia and dystonia across 10 to 12 years follow-up. Off periods affected 35.0% (95% CI 33.0, 37.0) at 4 to 6 years and 59.0% (55.6, 62.3) at 8 to 10 years, while dyskinesia affected 18.5% (16.9, 20.2) at 4 to 6 years and 42.1% (38.7, 45.5) at 8 to 10 years (Figures 1 and 2). 13.4% (12.1, 14.9) had painful off-state dystonia at 4 to 6 years, compared with 22.8% (20.1, 25.9) at 8 to 10 years. Off periods generally emerged as the first motor complication, with the subsequent development of dyskinesia. Dyskinesia was more

common in patients with off periods, but was also present in patients without off periods (Supplementary Tables 1 and 2).

Off periods and dyskinesia were mostly graded as ‘slight to mild’ throughout. Off periods caused greater functional impact than dyskinesia (Figures 1b and 2), and the impact was more likely to be graded as moderate-to-severe for off periods than dyskinesia (Figures 1c and 2). Motor fluctuations were complex in 33.5% (31.6, 35.5) at 4-6 years and 55.7% (52.3, 59.0) at 8-10 years (Figure 2e).

*Associated demographic and clinical factors*

In the univariable modelling, 12 factors for off periods, 14 factors for dyskinesia and 8 factors for off-state dystonia had a P value < 0.05 for one or more time duration. In the multivariable model, 9 factors for off periods, 11 factors for dyskinesia, and 7 factors for off-state dystonia had a P value < 0.05 for one or more time duration (Figure 3, Supplementary Tables 3 – 5, Supplementary Figure 5). Higher LEDD at assessment was associated with all 3 motor complications throughout, while younger age was associated with all 3 motor complications except for off periods and dyskinesia at 10-12 years disease duration (Figures 3 and 4). Given the loss of power indicated by the wider 95% confidence intervals at 10 to 12 years, it is likely that younger age would be associated with off periods and dyskinesia as a larger number of subjects reach this temporal milestone.

Dopaminergic responsiveness was significant for multiple time durations for each motor complication (Figure 5). Additional factors significantly associated with each of the 3 motor complications for at least one time duration were female gender and

higher MDS-UPDRS parts 1 and 2 scores (Figure 3, Supplementary Figure 5). For off periods, additional significantly associated factors included higher education, presence of anxiety, and a lower tremor score. For dyskinesia, additional significantly associated factors were higher GRS, lower BMI, lower tremor score, slower motor progression, and Hoehn and Yahr stage of 3 or greater. For off-state dystonia, Hoehn and Yahr stage of 3 or greater was the only additional significantly associated factor (Supplementary Figure 5).

The significant associations emerged as early as 2 to 4 years from diagnosis: for dyskinesia the factors included female gender ($P < 0.001$), younger age at diagnosis ($P = 0.018$), a higher MDS-UPDRS part 2 score ($P = 0.012$), lower MDS-UPDRS part 3 tremor sub-score ($P = 0.039$), LEDD ($P < 0.001$) and the Parkinson's GRS ($P = 0.026$). For off periods the values were younger age at diagnosis ($P < 0.001$), higher MDS-UPDRS part 1 ($P = 0.045$) and part 2 scores ($P < 0.001$) and LEDD ($P < 0.001$). For off-state dystonia the values were younger age at diagnosis ($P < 0.001$), female gender ($P = 0.002$), LEDD ($P < 0.001$), and higher MDS-UPDRS part 1 ($P < 0.001$) and Hoehn and Yahr ($P = 0.016$) scores (Figure 3, Supplementary Figure 5). Certain temporally constant factors, such as age and gender, may be interpreted as 'risk factors' for the development of motor complications, in contrast to clinical scores and LEDD, which change over time. In early disease, the motor complications odds ratios associated with an 100mg/d increase in LEDD were higher than in late disease. For off periods and dyskinesia this is unlikely to be due to chance as confirmed by a linear meta regression of the logistic regression coefficients on the time band midpoints (off periods $P = 0.030$; dyskinesia $P = 0.075$; dystonia $P = 0.48$).

This finding might, however, be due to higher absolute doses in later disease or loss to follow-up (Table 1).

Testing for first-order interactions revealed a potential interaction of age at diagnosis and LEDD in their association with motor fluctuations ($P < 0.02$ for 3 out of 5 time bands) and dystonia ($P < 0.08$ in 4 out of 5 time bands) with a stronger association between LEDD and motor fluctuations and dystonia in subjects who are younger at diagnosis (Supplementary Table 6). All other age interaction terms were found to be consistent with chance. Factors associated with motor complications were found to be consistent between males and females (Supplementary Table 7).

There was a cumulative effect of having multiple risk factors for each of the motor complications. Multiple associations found in the univariable models remained significant in the multivariable models. The multivariable models allow a meaningful distinction between subjects with low and high probability of motor complications (Figure 6). In early disease (2-4 years) < 10% of the q1 to q4 patients experience dyskinesia or off-state dystonia, while in q5 the prevalence of dyskinesia and off-state dystonia exceeds 20%. Throughout the 12 years the prevalence of off-state dystonia remains < 20% in the 60% of subjects with the advantageous associated demographic and clinical factors (q1 to q3), while it exceeds 50% at 10-12 years in those with the disadvantageous associated features (q5). While these results should not be viewed as model validation, they do show the potential of predicting the risk of future motor complications at a patient level.

## *Discussion*

We have combined three large international multicenter cohort studies following 3,343 patients for up to 12 years to undertake the largest prospective study of motor complications in Parkinson's disease to date. This has enabled us to quantify the presence, severity and functional impact of motor complications and define their associated demographic and clinical factors with greater detail and precision than possible from prior smaller studies.

*Presence*

By around five years, just over one third of patients develop off periods and fewer than one in five patients have dyskinesia. By around 9 years, 59.0% experience off periods and 42.1% develop dyskinesia. The consistently higher prevalence of motor fluctuations over dyskinesia in our study reflects the known natural history of PD, in which wearing off manifests as the first motor complication with the subsequent evolution of dyskinesia[1] (Supplementary Tables 1 and 2). Our findings are similar to the results of previous studies, in which rates of 40 to 54% for off periods, and 15 to 24% for dyskinesia were reported at 4 to 6 years[3, 5, 6]. In comparison to the PINE study, however, we identified a higher prevalence of motor fluctuations (35% vs. 21.3%) and less dyskinesia (18.5% vs. 28.4%) at 4 to 6 years[4], although the 95% CIs from PINE, a considerably smaller community-based PD cohort (183 vs. 3,343 PD patients) are consistent with our results. In an earlier interim analysis of the Oxford Discovery cohort, off periods affected 34.7% and dyskinesia 25.3% of 734 patients followed for up to 10 years[7]. We additionally demonstrate that painful off-

state dystonia affects 13.4% by around 5 years and 22.8% by around 9 years, while noting that dystonia is expressed as a proportion of off time.

*Severity and impact*

We show that when dyskinesia is present it has a longer duration than off time, but paradoxically the functional impact of off time is greater. This is consistent with prior reports of dyskinesia being largely 'non-disabling'[5, 6], and with the earlier interim analysis of the Oxford Discovery study[7].

*Associated demographic and clinical factors*

We confirm the significant independent relationship between the predisposing factors of higher LEDD, younger age and female gender and the occurrence of dyskinesia and off periods, in keeping with other studies of a similar design[4, 5, 7, 9-12]. Our study provides evidence that the strength of the association between each motor complication and LEDD becomes weaker with increasing disease duration. This may be attributed to relative differences in the absolute dose in early compared to late-stage disease or may reflect loss to follow-up during the later time periods. A significant novel finding is that painful off-state dystonia shares these 3 key factors.

The relationship between a higher LEDD and a greater probability of off periods in our study and others[7, 9, 10, 13, 24] might appear paradoxical, because dose increases are used to alleviate off periods in clinical practice. This may reflect the observation that patients with more dopa responsive disease are more likely to develop motor complications and therefore have incremental doses increases, whereas patients with lesser responsiveness are less likely to have up-titration of their dose. This

theory is substantiated by our prior observation that definite therapy responders have significantly higher LEDDs and improved MDS-UPDRS part 3 scores, in comparison to limited responders[25].

A novel aspect of this analysis is the assessment of gender- and age-specific factors associated with motor complications. This may reflect genetic factors predisposing patients both to younger age at diagnosis and greater susceptibility to motor fluctuations and dystonia with a higher LEDD. Although female gender was associated with a greater likelihood of motor complications, this analysis did not reveal any gender-specific predictors of motor complications in females compared with males.

Across the 3 cohorts, a subset of cases underwent dopaminergic challenge tests. Greater dopaminergic responsiveness by challenge test was significantly associated with higher rates of dyskinesia, off periods and painful off-state dystonia. Whilst previous reports have identified an association between dopaminergic responsiveness (by challenge test) and motor complications, the challenge tests were undertaken in significantly smaller patient cohorts[26, 27]. A clinician's subjective assessment of treatment response may be adequate to grade this therapy response, as an association with both dyskinesia and off time was found in cases with a strong L-dopa response based on case record review[28] and based on improvement scored on a 7-point Likert scale[7]. We plan a separate report comparing subjective interpretation of the dopaminergic response, and measured responses by challenge test.

Our analysis identified a significant association between the Parkinson's genetic risk score and dyskinesia ($0.026 \leq P \leq 0.50$ across all 2-year time intervals), but not with off periods ($0.095 \leq P \leq 0.95$) or dystonia. Whilst this corroborates an earlier analysis identifying an association between a higher GRS and dyskinesia[29], given the range in P values, it is possible that this finding may reflect a type I error due to multiple testing. Genetic determinants of dyskinesia have been reported, both for rare monogenic forms of Parkinson's[30], and for variants in dopamine receptor genes[31]. Given the current finding, we are now collaborating with a genetic meta-analysis of dyskinesia that will include functional genetic annotation, to corroborate this finding and better understand the nominated loci.

In our analysis, a higher MDS-UPDRS part 1 score evaluating non-motor features, was significantly associated with off-state dystonia, off periods and dyskinesia. This is consistent with prior studies[7, 13], and the interpretation in an earlier report that low mood and anxiety were key contributors to this relationship[7].

We found that dyskinesia, but not off periods or off-state dystonia, was significantly associated with lower BMI at assessment as in previous studies[7, 9, 32]. Although this may partly relate to a higher LEDD per kilogram of body weight, it showed an independent association perhaps reflecting weight loss secondary to the metabolic effects of dyskinesia.

In combining three large prospective cohort studies, this is the largest study evaluating motor complications in PD to date. This allowed us to undertake a detailed novel assessment of the factors related to dystonia for which prior studies

were underpowered to comprehensively assess separately from motor fluctuations and dyskinesia. Although there were some minor differences between the three cohorts, they were broadly similar with comparable demographic features to other published studies[3-5, 7].

Although this analysis involves multicenter international data from the US, UK, Europe, and Australia, included cases were predominantly Caucasian and recruited from specialist centers in Anglo-Saxon countries, which may limit the generalizability of our results. Furthermore, age at diagnosis in these observational datasets is slightly higher, as expected, to that reported for PD patients recruited to clinical trials, so age-specific rates should be used if these data were to be used to power future clinical trials. A further potential limitation is that the PD diagnosis was clinical rather than pathological, although functional dopaminergic imaging was used to confirm dopamine depletion either as a routine part of the study protocol (PPMI) or in clinically uncertain cases (*Discovery* and *Tracking)*, thereby excluding more benign disorders. Additionally, ongoing diagnostic review was undertaken at follow-up visits against defined criteria of atypical features. Overdiagnosis of MSA and PSP may occur when the levodopa responsiveness is limited, where PD is the actual diagnosis at autopsy[33]. It is therefore possible that patients with less levodopa responsive PD were excluded from these cohorts, resulting in a slight overestimation of motor complications. Overdiagnosis of PD in cases without confirmatory functional dopaminergic imaging would have the opposite effect. Like any longitudinal study, there is loss to follow-up either due to death, mobility outside the study area or increasing disease severity, which will in some cases result in patients and/or carers wishing to withdraw. Our observations in the later time-periods could therefore be

biased if withdrawal is related to motor complications. In this case our prevalence estimates in later time-periods will underestimate the true prevalence in the target population.

Whilst the MDS-UPDRS part 4 is a standardized objective method of evaluating motor complications, it does not differentiate between motor and non-motor wearing off to allow these to be analyzed separately and is less sensitive at detecting motor fluctuations in early disease, which may have underestimated their true prevalence during the earlier stages of follow-up. Furthermore, we did not analyze non-troublesome and troublesome dyskinesia separately, the latter of which could impact more significantly upon functional status and quality of life. Finally, it is possible that multiple testing gave rise to type I errors, particularly in the case of the Parkinson's GRS and its association with early dyskinesia, given the wider range of P values.

In summary, we found that off periods are significantly more common and consistently lead to greater functional impairment than dyskinesia during the first 12 years of PD. We have additionally confirmed previous associations between motor complications and predisposing factors, adding key observations about off-state dystonia, dopaminergic responsiveness, and the genetic risk score and its relationship to dyskinesia.

**Acknowledgements:**

We would like to thank Dr Manuela MX Tan at the Department of Clinical and Movement Neurosciences, University College London, and Dr Stephanie Millin at the Oxford Parkinson's Disease Centre, University of Oxford, for their assistance with cleaning and imputing the genetic data in the *Tracking Parkinson's* and *Oxford Discovery* studies, respectively.

*PPMI:* This analysis uses data openly available from PPMI (Tier 1) and genetic data obtained from PPMI upon request (Tier 2). Data used in the preparation of this article were obtained in November 2022 from the Parkinson's Progression Markers Initiative (PPMI) database (www.ppmi-info.org/access-data-specimens/download-data), RRID:SCR_006431. For up-to-date information on the study, visit www.ppmi-info.org.

Funding: PPMI – a public-private partnership – is funded by the Michael J. Fox Foundation for Parkinson's Research and funding partners, including 4D Pharma, Abbvie, AcureX, Allergan, Amathus Therapeutics, Aligning Science Across Parkinson's, AskBio, Avid Radiopharmaceuticals, BIAL, Biogen, Biohaven, BioLegend, BlueRock Therapeutics, Bristol-Myers Squibb, Calico Labs, Celgene, Cerevel Therapeutics, Coave Therapeutics, DaCapo Brainscience, Denali, Edmond J. Safra Foundation, Eli Lilly, Gain Therapeutics, GE HealthCare, Genentech, GSK, Golub Capital, Handl Therapeutics, Insitro, Janssen Neuroscience, Lundbeck, Merck, Meso Scale Discovery, Mission Therapeutics, Neurocrine Biosciences, Pfizer, Piramal, Prevail Therapeutics, Roche, Sanofi, Servier, Sun Pharma Advanced Research Company, Takeda, Teva, UCB, Vanqua Bio, Verily, Voyager Therapeutics, the Weston Family Foundation and Yumanity Therapeutics

*Tracking Parkinson's:* This work was supported by Parkinson's UK [grant number J-1101].

*Oxford Discovery*: This work was supported by Parkinson's UK [grant number J-2101- 'Understanding Parkinson's Progression']. The authors thank the participants and their families for their involvement in this project, Parkinson's UK for funding the research, and the Dendron team for supporting data collection. Clinical data collected in the Discovery cohort is managed using REDCap[34, 35].

**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.

**SEG:** 2C, 3A, 3B;

**TZ:** 2A, 2B, 2C, 3A, 3B;

**AN:** 2C, 3B;

**MAL:** 2A; 2C, 3B;

**VM:** 2C, 3B;

**FAH:** 1C, 3C;

**KAG:** 1A, 1B, 1C, 2C, 3A, 3B;

**HRM:** 1A, 1B, 1C, 2C, 3B;

**MTH:** 1A, 1B, 1C, 3B;

**YBS:** 1A, 1B, 1C, 2A, 2C, 3B;

**DGG:** 1A, 1B, 1C, 2C, 3A, 3B.

**Disclosures:**

**Funding sources and Conflict of Interest:**

MAL received consultancy fees for advising on a secondary analysis of an RCT sponsored by North Bristol NHS trust.

VM has received honoraria from BIAL Pharma, AbbVie and Britannia Pharmaceuticals.

KAG has received consultancy fees from Parkinson's UK.

HRM is employed by UCL. In the last 12 months he reports paid consultancy from Roche, Aprinoia, AI Therapeutics and Amylyx; lecture fees/honoraria - BMJ, Kyowa Kirin, Movement Disorders Society. Research Grants from Parkinson's UK, Cure Parkinson's Trust, PSP Association, Medical Research Council, Michael J Fox Foundation.

HRM is a co-applicant on a patent application related to C9ORF72 - Method for diagnosing a neurodegenerative disease (PCT/GB2012/052140).

MTH received funding/grant support from Parkinson's UK, Oxford NIHR BRC, University of Oxford, CPT, Lab10X, NIHR, Michael J Fox Foundation, H2020 European Union, GE Healthcare and the PSP Association. She also received payment for Advisory Board attendance/consultancy for Lundbeck, ESCAPE Bio, Evidera, Manus Neurodynamica, Biogen MA, CuraSen Therapeutics, Roche Products Ltd, JAZZ Pharma, Aventis Pharma. She is an advisory founder of NeuHealth Digital Ltd (company number: 14492037), a digital biomarker platform to remotely manage condition progression for Parkinson's.

YBS has received consultancy fees from Human Centric DD and Parkinson's UK.

DGG has received honoraria from BIAL Pharma, Britannia Pharmaceuticals, and

UCB Pharma, consultancy fees from NeuroClin Glasgow, and both consultancy fees and grant support from Parkinson's UK.

The other co-authors declare that there are no additional disclosures or conflicts of interest to report.

**Financial disclosures for the previous 12 months:**

MAL received consultancy fees for advising on a secondary analysis of an RCT sponsored by North Bristol NHS trust.

VM has received funding for travel to a conference for BIAL and lecture fees from BIAL.

HRM has received paid consultancy from Roche, Aprinoia, AI Therapeutics and Amylyx; lecture fees/honoraria - BMJ, Kyowa Kirin, Movement Disorders Society. Research Grants from Parkinson's UK, Cure Parkinson's Trust, PSP Association, Medical Research Council, and the Michael J Fox Foundation.

MTH is an advisory founder of NeuHealth Digital Ltd (company number: 14492037), a digital biomarker platform to remotely manage condition progression for Parkinson's.

YBS has received consultancy fees from Human Centric DD and Parkinson's UK.

KAG has received consultancy fees from Parkinson's UK.

DGG has received consultancy fees from Parkinson's UK and NeuroClin Glasgow.

The other co-authors declare that there are no additional disclosures to report.

**Ethical compliance statement:**

*PPMI* was conducted following approval of the local ethics committees of the participating sites. The West of Scotland Research ethics committee and the local National Health Service (NHS) research ethics committee approved the *Tracking Parkinson's* and *Oxford Discovery* studies, respectively. All three studies were

conducted in accordance with national legislation and the Declaration of Helsinki. Written informed consent was obtained from each participant prior to enrollment. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

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631 ***Legends for figures***

632

633 **FIG. 1.** Presence and functional impact of motor complications over time in 3343

634 patients with Parkinson's disease.

635 **Legend:** Off periods were consistently more common than dyskinesia and dystonia

636 (A). Off periods caused greater functional impact (B) and was more likely to be

637 graded as moderate-to-severe (C) than dyskinesia. The error bars indicate Wilson

638 95% confidence intervals.

639

640 **FIG. 2.** Severity of motor complications and their functional impact over time in 3343

641 patients with Parkinson's disease.

642 Legend: The prevalence and severity of motor complications increased over time (A,

643 C and F). Off periods were the most prevalent motor complication (C). Their

644 complexity increased over time (E) and they caused greater functional impact than

645 dyskinesia (B and D).

646

647 **FIG. 3.** Odds ratios from univariable and multivariable logistic regression for the main

648 covariates.

649 Legend: Error bars indicate 95% confidence intervals.

650 GRS: genetic risk score; LEDD: levodopa equivalent daily dose; MDS-UPDRS:

651 Movement Disorder Society Unified Parkinson's Disease Rating Scale.

652

653

**FIG. 4.** Prevalence of motor complications with subjects categorized according to selected demographic and clinical features.

**Legend:** Motor complications were more prevalent in younger patients, females, with higher LEDD and greater motor responsiveness (≥ 24.5% improvement defined as a definite dopaminergic response). Error bars indicate 95% confidence intervals.

BMI: body mass index; LEDD: levodopa equivalent daily dose.

**FIG. 5.** Odds ratios for dopaminergic responsiveness from secondary bivariable logistic regression

Legend: Dopaminergic responsiveness was significantly associated with motor complications. * The multivariable model uses the logit of the predicted probabilities from the main multivariable model, with responsiveness as a covariate. Error bars: 95% confidence intervals.

**FIG. 6.** Prevalence of motor complications by quintiles of probabilities as estimated by the lasso models.

Legend: The multivariable models meaningfully distinguish between subjects with low and high probability of motor complications. Cases were allocated to quintiles according to their model estimated probability of motor complications (q1 – q5) and the observed prevalence of motor complications was compared.

Supplementary Figures 1 – 4: Comparison of the demographic and clinical features of the three cohorts

Legend: Minor differences were identified between the three cohorts, but they were broadly homogenous. In comparison to the *Tracking Parkinson's* and *Oxford*

*Discovery* cohorts, PPMI cases were generally younger, with higher MoCA scores, less progression on the MDS-UPDRS part 3, and more frequent use of amantadine (Supplementary Figures 2, 3 and 4). The *Tracking Parkinson's* cohort had higher rates of anxiety and depression, and a greater proportion of cases with a Hoehn and Yahr score of 3 (Supplementary Figure 4).

APOE4: apolipoprotein E4 allele; BMI: body mass index; COMTI: catechol-O-methyltransferase inhibitor; DA: dopamine agonist; Dopaminergic resp: dopaminergic responsiveness; GRS: genetic risk score; HY 3: Hoehn and Yahr stage 3; LEDD: levodopa equivalent daily dose; MAOBI: monoamine oxidase type B inhibitor; MoCA: Montreal Cognitive Assessment; MDS-UPDRS: Movement Disorder Society Unified Parkinson's Disease Rating Scale.

Supplementary Figure 5: Odds ratios from univariable and multivariable logistic regression for all covariates

Legend: Error bars indicate 95% confidence intervals.

BMI: body mass index; HY 3 or greater: Hoehn and Yahr stage 3 or greater; MDS-UPDRS: Movement Disorder Society Unified Parkinson's Disease Rating Scale

696 ***Tables***

**TABLE 1:** Demographic and clinical features of the *Tracking Parkinson's*, *Oxford Discovery* and *PPMI* cohorts

| | **Duration of Parkinson's disease in years** | | | | | |
|---|---|---|---|---|---|---|
| | 0-2 | 2-4 | 4-6 | 6-8 | 8-10 | 10-12 |
| **Number of cases**[a-b] | 2538 | 2935 | 2232 | 1452 | 829 | 348 |
| **Age at diagnosis** | 65.6 (9.8) | 65.2 (9.4) | 64.3 (9.3) | 63.0 (8.9) | 61.7 (8.6) | 60.1 (8.8) |
| **Age** | 66.7 (9.8) | 68.2 (9.4) | 69.2 (9.3) | 69.9 (8.9) | 70.6 (8.6) | 70.8 (8.8) |
| **Male, n (%)** | 1652 (65.1) | 1890 (64.4) | 1434 (64.3) | 948 (65.3) | 546 (65.9) | 226 (64.9) |
| **Education >12 years, n (%)** | 1653 (67.1) | 1945 (67.4) | 1558 (70.5) | 1063 (73.7) | 627 (75.9) | 266 (76.7) |
| **BMI** | 27.0 (4.6) | 27.0 (4.7) | 26.8 (4.9) | 26.6 (4.9) | 26.3 (5.4) | 26.8 (6.2) |
| **Dopa responsiveness** | 28.9 (21.3) | 29.2 (21.9) | 30.2 (21.8) | 29.3 (21.3) | 29.4 (21.7) | 27.4 (20.5) |
| **MDS-UPDRS 1 total** | 8.6 (5.1) | 10.0 (5.8) | 11.0 (6.2) | 11.7 (6.2) | 12.5 (6.4) | 12.7 (6.7) |
| **Depression, UPDRS 1 > 0, n (%)** | 838 (33.1) | 1030 (35.1) | 853 (38.3) | 586 (40.6) | 365 (44.0) | 144 (41.4) |
| **Anxiety, UPDRS 1 > 0, n (%)** | 1095 (43.2) | 1277 (43.6) | 996 (44.7) | 702 (48.5) | 414 (49.9) | 172 (49.6) |
| **MDS-UPDRS 2 total** | 8.8 (6.1) | 11.0 (7.1) | 13.0 (7.8) | 14.2 (8.0) | 15.5 (8.3) | 16.0 (8.6) |
| **MDS-UPDRS 3 total** | 23.9 (11.9) | 27.5(13.5) | 30.0 (15.1) | 31.3 (15.6) | 32.0 (16.7) | 31.9 (16.5) |
| **MDS-UPDRS 3 progression**[c] | 1.9 (1.2) | 1.9 (1.3) | 1.8 (1.4) | 1.6 (1.4) | 1.5 (1.3) | 1.2 (1.2) |
| **MDS-UPDRS 4 total** | 0.4 (1.3) | 1.0 (2.1) | 2.0 (3.0) | 3.0 (3.5) | 4.0 (3.9) | 4.6 (4.2) |
| **N (%) with dyskinesia** | 64 (2.5) | 249 (8.5) | 409 (18.5) | 444 (30.8) | 342 (42.1) | 177 (51.3) |
| **N (%) with functional impact from dyskinesia** | 34 (1.4) | 111 (3.9) | 203 (9.3) | 222 (15.6) | 199 (24.7) | 100 (29.0) |
| **N (%) with off periods** | 223 (9.0) | 559 (19.4) | 770 (35.0) | 673 (47.0) | 480 (59.0) | 215 (62.7) |
| **N (%) with functional impact from motor fluctuations** | 191 (7.6) | 488 (16.7) | 666 (30.2) | 590 (41.1) | 423 (51.7) | 187 (54.4) |

| | | | | | | |
|---|---|---|---|---|---|---|
| **N (%) with complex motor fluctuations** | 207 (8.3) | 540 (18.6) | 733 (33.5) | 636 (44.6) | 456 (55.7) | 210 (60.9) |
| **N (%) with painful off-state dystonia** | 113 (4.6) | 243 (8.5) | 291 (13.4) | 260 (18.3) | 183 (22.9) | 83 (24.7) |
| **Medication** | | | | | | |
| **L-dopa, n (%)** | 1340 (52.8) | 2234 (76.3) | 1976 (88.9) | 1359 (94.0) | 799 (96.6) | 339 (97.4) |
| **Dopamine agonist, n (%)** | 606 (23.9) | 1095 (37.4) | 964 (43.4) | 653 (45.2) | 417 (50.4) | 166 (47.7) |
| **MAOB-I, n (%)** | 581 (22.9) | 1012 (34.6) | 851 (38.3) | 596 (41.2) | 376 (45.5) | 148 (42.5) |
| **COMT-I, n (%)** | 35 (1.4) | 168 (5.7) | 238 (10.7) | 211 (14.6) | 160 (19.4) | 78 (22.4) |
| **Amantadine, n (%)** | 25 (1.0) | 90 (3.1) | 117 (5.3) | 113 (7.8) | 103 (12.5) | 66 (19.1) |
| **LEDD** | 240.4 (192.0) | 428.1 (254.0) | 582.4 (307.0) | 690.7 (356.3) | 822.0 (392.4) | 908.1 (464.4) |
| **DBS, n (%)** | 0 (0.0) | 2 (0.1) | 6 (0.3) | 15 (1.0) | 21 (2.5) | 14 (4.0) |
| **MoCA** | 25.4 (3.4) | 25.3 (3.8) | 25.4 (4.0) | 25.8 (4.0) | 26.0 (4.0) | 26.3 (4.1) |
| **Hoehn and Yahr > 2, n (%)** | 154 (6.1) | 321 (11.1) | 331 (15.3) | 227 (17.4) | 137 (20.8) | 75 (27.2) |
| **APOE ε4+, n (%)** | 587 (26.5) | 668 (26.0) | 497 (25.1) | 287 (22.2) | 165 (22.1) | 61 (18.9) |
| **Genetic risk score PD**[d] | 0.00 (1.0) | -0.01 (1.0) | 0.02 (1.0) | 0.06 (1.0) | 0.13 (1.0) | 0.11 (1.0) |

APOE ε4: apolipoprotein E ε4 allele; COMT-I: Catechol-O-methyltransferase inhibitor; DBS: deep brain stimulation; GRS: genetic risk score; LEDD: levodopa equivalent daily dose; MAOB-I: Monoamine oxidase inhibitor type B; MoCA: Montreal Cognitive Assessment.

[a]Fewer cases are present at 0-2 years than 2-4 years as some cases were recruited at a disease duration >2 years.

[b]Cases were included when at least one of the MDS-UPDRS 4 scores was recorded.

[c]The MDS-UPDRS part 3 progression is expressed as points/per year.

[d]Z-scored.