Differences in the Presentation and Progression of Parkinson's Disease by Sex

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Sex differences in Parkinson's disease

Abstract

Background: Previous studies reported various symptoms of Parkinson's disease (PD) associated with sex. Some were conflicting or confirmed only in one study.

Objectives: To examine sex associations to PD phenotypes cross-sectionally and longitudinally in large scale data.

Methods: We tested 40 clinical phenotypes, using longitudinal, clinic-based patient cohorts, consisting of 5,946 patients, with a median follow-up of 3.1 years. For continuous outcomes, we used linear regressions at baseline to test sex-associated differences in presentation, and linear mixed-effects models to test sex-associated differences in progression. For binomial outcomes, we used logistic regression models at baseline and Cox regression models for survival analyses. We adjusted for age, disease duration, and medication use. In the secondary analyses, data from 17,719 PD patients and 7,588 non-PD participants from an online-only, self-assessment PD cohort were cross-sectionally evaluated to determine whether the sex-associated differences identified in the primary analyses were consistent and unique to PD.

Results: Female PD patients had a higher risk of developing dyskinesia early during the follow-up period, with a slower progression in activities of daily living difficulties, and a lower risk of developing cognitive impairments compared with male patients. The findings in the longitudinal, clinic-based cohorts were mostly consistent with the results of the online-only cohort.

Conclusions: We observed sex-associated contributions to PD heterogeneity. These results highlight the necessity of future research to determine the underlying mechanisms and importance of personalized clinical management.

Keyword:

Parkinson's disease; gender; sex; dyskinesias; cognitive impairment; activities of daily livings;

Main text

Introduction

The prevalence of Parkinson's disease (PD) is 1.5–2.0 times higher in men than in women. This discrepancy suggests the potential existence of sex-associated factors that modify the disease process. Identifying the interplay between sex and PD has the potential to assist the development of disease-modifying therapy, inform patient management strategies, and allow the planning of more efficient clinical trials. Researchers have previously investigated sex-associated differences in phenotypes among patients with PD.[1–3] Male PD patients have been reported to present akinesia/rigid features,[4] cognitive impairment,[5–7] daytime sleepiness,[8] and rapid eye movement (REM) sleep behavioral disorder (RBD) more frequently than female PD patients.[9,10] In contrast, anxiety disorder/depression[11–14] and dyskinesia[11,15–17] were documented to occur more frequently in female PD patients than in male PD patients. However, these studies were generally small in sample size and predominantly performed in a cross-sectional setting.

In this study, we analyzed longitudinal data from 12 PD cohorts, representing 5,946 participants, with a median of 3.1 years of follow-up. This study had two objectives: (1) to identify the baseline differences between men and women, in terms of disease presentation, and (2) to identify the influences of sex on longitudinal symptom trajectory. Further, we analyzed the Fox Insight dataset, an online-only, PD research cohort, to assess whether the observations made using the longitudinal datasets were consistent in an independent dataset. Moreover, by analyzing the data from both PD participants and non-PD participants in the Fox Insight dataset, we were able to evaluate differences in the prevalence of self-reported outcomes between participants with and without PD. This analysis further illustrated that some of the identified differences may be influenced by general differences between males and females, whereas others are disease-specific.

Methods

Participants

12 longitudinal cohorts

We analyzed data from 12 longitudinal PD cohorts, from North America, Europe, and Australia, in this study (Table 1). Among these cohorts, the following four studies enrolled people with early-phase PD who were not being treated at the time of study enrollment (de novo cohorts): Parkinson's Progression Markers Initiative (PPMI), Parkinson Research Examination of CEP-1347 Trial study and its subsequent prospective study (PreCEPT/PostCEPT), the Norwegian ParkWest study (PARKWEST), and Deprenyl and Tocopherol Antioxidative Therapy of Parkinsonism (DATATOP). Other cohorts included Parkinsonism Incidence and Cognitive and Non-motor heterogeneity In Cambridgeshire (PICNICS), National Institutes of Health Exploratory Trials in Parkinson's Disease Large Simple Study 1 (NET_PD_LS1), Drug Interaction With Genes in Parkinson's Disease (DIGPD), Parkinson's Disease Biomarker Program (PDBP), Harvard Biomarkers Study (HBS), ParkFit Study (PARKFIT), Profiling Parkinson's Disease Study (PROPARK), and Udall Centers program (UDALL_PENN). Participants' information was obtained under appropriate written consent and with local institutional and ethical approval. The summary of the designs and inclusion/exclusion criteria applied to these cohorts are documented in the Supplemental Materials. The study protocols were approved at the local institutional review boards and the participants provided written informed consent.

Fox Insight

To evaluate the consistency of results from the longitudinal dataset, we explored an independent dataset, Fox Insight. Fox Insight is an online-only, PD research cohort.[18] The details of the study are available online (https://foxinsight.michaeljfox.org/). Individuals, aged 18 or older, with and without PD, were enrolled through in-person referral or online advertisements. The participants provided online informed consent, and self-reported demographic,

characteristics, symptoms, medical history, and PD medication data were collected. Although Fox Insight is a longitudinal study, we analyzed the data cross-sectionally for the present study because the follow-up periods were relatively short (e.g., the median follow-up period was 0.4 years for Non-Motor Symptoms Questionnaire). During the analysis step, we adjusted for age and disease duration. To limit the impacts of the extreme data points, we included participants from the middle 80% of the age distribution and the disease duration distribution (only among PD participants), which excluded any participants younger than the lower 10th percentile (< 46.8 years old) or older than the 90th percentile (> 77.4 years old) and PD patients with a disease duration shorter than one year (10th percentile) and longer than 13.5 years (90th percentile).

Measurements

Clinical Data Harmonization Among the 12 cohorts

Twenty-three measurements, 11 binomial and nine continuous measurements, were analyzed as outcome measures. Binomial outcomes included constipation, mild cognitive impairment, depression, daytime sleepiness, hyposmia, insomnia, wearing off, dyskinesias, RBD, restless-leg syndrome, and modified Schwab and England Activities of Daily Living Scale scores of 70 or lower (SEADL70). Some binomial outcomes had study-specific outcomes, and these criteria are summarized in the Supplemental Materials. For continuous outcomes, we collected the Hoehn and Yahr (HY) stage scale, total and sub-scores for the Unified Parkinson's Disease Rating Scale (UPDRS) or the Movement Disorder Society–revised version (MDS-UPDRS), Mini-Mental State Examination, Montreal Cognitive Assessment (MoCA), and modified Schwab and England Activities of Daily Living Scale (SEADL). UPDRS scores were normalized to the z-values (UPDRS*_scaled).

Fox Insight

The February 2020 data was downloaded from https://foxden.michaeljfox.org. The demographic and disease status data were obtained from enrollment and registration questionnaires. For clinical outcomes of interest, we obtained the responses from the following questionnaires: Geriatric Depression Scale (GDS) for depression (score of six or higher);[19] Non-Motor Symptoms Questionnaire (NMS-QUEST) for constipation, depressed mood (Mood depressed) and a proxy for lack of the sense of smell/taste;[20] MDS-UPDRS Part II questionnaire; REM Sleep Behavior Disorder Single-Question Screen;[21] 15-item Penn Parkinson's Disease Daily Activities Questionnaire (PDAQ-15) for cognition-related instrumental functional abilities;[22] and Understanding the Impact of Off and On in Parkinson's Patients Questionnaire for dyskinesia and wearing off.

Statistical analysis

Linear and logistic models were used to analyze baseline differences in PD presentation between male and female patients, per cohort. For binomial outcomes, a minimum of 25 outcomes should be observed in the analyzed cohort. Covariates were the linear and square terms of age and disease duration, to adjust for linear and non-linear effects. In addition, we adjusted for levodopa and dopamine agonist use. To test differences in the progression rates among continuous outcomes, we used linear mixed-effects models, with the same covariates as the baseline models and random effects on the individual intercept and slope (change per year). We evaluated sex-associated differences in progression rates by testing the interaction between sex and disease duration. Survival analyses were conducted among those who did not have an outcome at baseline. Cox regression models were used, adjusting for the same covariates as those used in the baseline models. Any outcomes with fewer than 20 events over the follow-up period were not analyzed. The R model statements for these analyses are summarized in the Supplemental Materials.

Then, we combined the cohort-level results with an inverse variance-weighted random-effect model. We focused on robust associations throughout the cohorts; therefore, meta-analyses with p-values less than 0.05 for a test of homogeneity

were excluded from further evaluations. Any associations with a two-sided p-value of 0.05, after Bonferroni-correction for the number of total analyses, were considered significant.

For the analysis of the Fox Insight dataset, we tested two terms: the mean difference between males and females (main term) and the interaction between sex and disease duration (interaction term). The adjusted covariates were linear and square age, linear and square disease duration, and indicators of levodopa and dopamine agonist usage. We further analyzed the association between sex and outcomes among non-PD participants, adjusted for linear and square age. Then, we conducted a test of homogeneity between sex-associated differences identified among PD cases and non-PD participants, to evaluate whether the sex differences were PD-specific or reflected differences observed in the non-PD population. In the analyses for this dataset, we used a significance level of 0.05 for the raw p-value because the purpose of these analyses was to evaluate consistency with the longitudinal analyses.

All the statistical analyses and drawings were executed using R version 3.6 and python version 3.7. The analysis scripts are available at https://github.com/neurogenetics/PDpheno_by_sex.

Results

The cohort participants are summarized in Table 1. Participants in these cohorts varied in age and PD stage; however, most participants were in relatively early PD phases. The majority of participants were of European descent. Fox Insight included more female participants than the other cohorts, and the ratio of females to males was especially high among non-PD participants, as previously described.[23] Moreover, we did not observe a significant difference in age of diagnosis between the men and the women among each cohort except for Fox Insight, in which the female patients had on average 0.61 (SD: 0.12) years younger age of diagnosis than the male patients. Interestingly, the age of non-PD participants in Fox Insight was also younger than male non-PD participants. The younger age of onset may be reflecting different age distributions of the study population by sex in Fox Insight. In the following analyses, we adjusted for age, disease duration and medications.

In total, we conducted 40 meta-analyses, using the clinic-based longitudinal data, three of which were rejected following a test of heterogeneity, with a significance level of 0.05. Using the Bonferroni correction of multiple comparisons, we set our p-value (P) threshold to 0.05/37 =0.00135. Among these associations, nine were significant, and the direction and magnitude of associations linked to being female compared with being male are shown in Table 2 and Figure 1/2. (All meta-analysis results can be found in Supplemental Materials).

Female PD patients were less likely to develop cognitive impairments over time {hazard ratio (HR) 0.65 [0.53, 0.79] (mean [95% confidence interval]), P = 2.1E-5} than male PD patients, and an even stronger association was observed when we adjusted for years of education (HR 0.59 [0.48, 0.73], P = 4.6E-7, Supplemental Material). This association remain significant when we further adjusted for the baseline MoCA score (HR 0.56 [0.37, 0.86], P = 0.007) or the baseline MMSE score (HR 0.67 [0.51, 0.90], P = 0.007, Supplemental Material) at the significance level of 0.05. Additionally, the baseline MoCA scores were higher in female patients (0.63 [0.27, 1.00]) than in male patients, whereas the baseline MMSE score was not significantly different between sexes (P = 0.97, Supplemental Materials).

Female patients presented with a higher rate of developing dyskinesia (HR 1.29 [1.16, 1.44]). To assess the impacts of weight, body mass index (BMI) and medication on this association, we conducted ad hoc analyses on a subset of data (PDBP, PPMI, and NET_PD_LS1: 2,281 participants) for which height at baseline, weight at baseline, and medication at visits were recorded. We adjusted the analyses for each of these factors. With the “weight” adjustment, the association was no longer significant (P = 0.058), whereas the magnitude of the association became larger when adjusted for levodopa dosages or levodopa equivalent dosages. Adjusting for BMI did not substantially change the magnitude of the association (Beta: from 0.284 to 0.249), and the sex difference remained still significant (Supplemental Materials). Consistent with the higher incidence rate of dyskinesia in female patients, female PD patients in non-de novo cohorts also presented more dyskinesia at baseline than male patients.

Activities of daily living (ADL), captured in the UPDRS Part II, were better in female PD patients than in male PD patients in the baseline analysis (-0.12 [-0.18, -0.06], in the z-score), and the progression rate was slower in female patients than in male patients (-0.14 [-0.20, -0.08] in z-score per year). We added post-hoc analyses of UPDRS Part II scores in the different versions separately. The baseline score differences (female-male) were -0.57 [-1.20, 0.06] (P = 0.07) in MDS-UPDRS and -0.52 [-0.82, -0.21] (P = 7.9E-4) in the original UPDRS. The differences in the progression rate were -0.81 [-1.18, -044] (P = 1.4E-5) in MDS-UPDRS and -0.43 [-0.71, -0.15] (P = 2.5E-3) in the original UPDRS. A more detailed analysis of the forest plots of the UPDRS Part II scores at baseline showed that the associations between sex and UPDRS Part II were not apparent among the de novo cohorts but, rather, were driven by differences observed in the non-de novo cohorts (Figure 1). Although we did not find significant sex-associated differences in progression rates in the UPDRS Parts I/III/IV, the rate of change for the total UPDRS scores was significantly milder in female patients than in male patients (-0.11 [-0.16, -0.06] per year, in the z-score). In the raw scores, the sex-associated difference (female-male) in rate of change in MDS-UPDRS total score (female-male) was -2.7 [-3.47, -1.95] (P = 2.3E -12) and that of the original UPDRS total score was -0.91 [-1.33, -0.49], (P = 2.66E-05). When only considering the de novo cohorts, similar results were reported for UPDRS part III, with a slower progression rate in female patients than in male patients (-0.14 [-0.21, -0.07] in z-score per year, P = 2.6E-5, Supplemental Materials). This was corresponding to -1.59 [-2.47, -0.71] (P = 4.6E-4) per year difference (female-male) in the rate of change in MDS-UPDRS Part III or -1.01 [-1.78, -0.24] (P = 0.01) per year in the original UPDRS Part III.

Finally, female patients also had lower scores on the UPDRS Part III and the UPDRS total score compared with male patients during the baseline analyses.

When analyzing similar phenotypes within the Fox Insight dataset, we generally confirmed the results of the longitudinal dataset analyses (Table 3). In the Fox Insight dataset analysis, the interaction terms between sex and disease duration indicated the average sex-associated differences in the longitudinal trajectories for the outcomes. For example, a positive association for the interaction between disease duration and PDAQ-15 indicated that the PDAQ-15 scores for female patients were higher than those in male patients (i.e., better cognition-related instrumental functional abilities) among

patients with longer disease durations in the Fox Insight dataset. To illustrate this, we visualized the sex differences, stratified by disease duration (Supplemental Materials). The results are consistent with those for the longitudinal dataset analysis, indicating that female patients had a lower risk of developing cognitive impairments during the disease course. Similarly, the results from the Fox Insight dataset were consistent with the increased rate of dyskinesia development among female patients compared with male patients, and the lower scores and a slower deterioration rate in UPDRS Part II among female patients, as observed in the longitudinal analyses.

In addition, null differences between male and female patients in the presentation and progression of wearing off, depression, and hyposmia were also supported by the Fox Insight dataset. In contrast, the loss of the sense of smell/taste was significantly more frequently reported in males among the control participants. Having PD might diminish the general sex difference associated with this phenotype.

Single question answers for RBD and some NMSQuest questionnaire questions regarding “difficult to stay awake” (NMSQ_Awake), “difficulty in getting to sleep” (NMSQ_Sleep), “feeling sad, low or blue” (NMSQ_Feel), and NMSQ_Constipation were significantly different according to sex in the Fox Insight dataset. The prevalences of similar outcomes, such as possible RBD, daytime sleepiness, insomnia, depression, and constipation, were not significantly associated with sex in the meta-analyses of 12 longitudinal cohorts. However, the test for these associations gives raw p-values less than 0.05, with the same directions as the Fox Insight results. The primary analyses may not have included large enough sample sizes to detect these associations. All of the sex-phenotype associations among PD participants, not significant in the longitudinal dataset but significant in the Fox Insight dataset, were also significant among non-PD participants. In addition, based on the test of homogeneity between the results from PD and non-PD participants, suggesting that the magnitudes of these sex-associated differences in PD participants did not differ from those in non-PD participants.

Discussion

We analyzed clinic-based, longitudinal data from 5,946 participants and meta-analyzed the differences in presentation and progression of phenotypes between men and women with PD. We also used web-based, online cohorts and analyzed data from 17,719 PD patients and 7,588 non-PD participants to confirm our results. The results suggested that female PD patients develop dyskinesia early, progress more slowly with respect to ADL restrictions, and are less likely to develop cognitive impairments. For some non-motor symptoms explored in the online questionnaires (such as possible RBD, daytime sleepiness, insomnia, depressive mood, and constipation), we found significant sex-associated differences among PD participants, only in the Fox Insight dataset. These unconfirmed sex-associated differences may not be specific to PD, as we also observed the same associations in the non-PD participants.

Some studies have previously reported that female patients demonstrated an increased risk of developing earlier and more severe dyskinesia[11,15] and a longer duration of dyskinesia.[16] These reports are consistent with the faster development of dyskinesia among female patients and the large rate of UPDRS Part IV score increases observed in our study. The reasons for this phenomenon are not fully understood, but the relatively higher levodopa dosages with respect to body weight in females may be partially responsible.[17] For example, the commonly used levodopa tablet contains 50 mg or 100 mg levodopa and this is relatively a larger jump for those with less weight, and that may result in stronger treatment for them compared with those with more weight. Our ad hoc analyses also suggested that body weight plays a role in the association between sex and the early development of dyskinesia.

Contradictory results have been reported previously with regards to sex-associated differences in ADL impacts. Two studies evaluated patients who underwent surgical treatment for PD. One study observed no differences in the UPDRS Part II scores between males and females, whereas the other study reported that females had worse scores than males. In these studies, females had a longer duration of disease, which may have affected the results. Another cross-sectional study also reported worse UPDRS Part II scores among female patients.[11] They reported that, among the five categories of overall ADL capacity, the two most-severe categories were more frequent among females than males, based on the results

of a chi-squared test, whereas our analyses used UPDRS Part II scores and multivariable regression models. These different outcome measurements and statistical approaches may account for different results.

The slower development of cognitive declines in female patients was reported by some longitudinal studies.[5,6,24] The executive and attention features were primarily affected in PD patients. While Alzheimer's disease, for which women confer more risk, is emphasized as disability in the memory feature, the executive and attention features are primarily affected in PD patients. MoCA is more sensitive for detecting dysfunctions in these areas than MMSE,[25] and this may be one of the reasons that we observed baseline difference in MoCA but not MMSE. In contrast, the longitudinal differences in the rates of decline for either the MoCA or MMSE were not significantly different between the two sexes, in our data. Interestingly, MoCA scores were sometimes reported to be higher in healthy aging women than in men.[26–28] The slower development of cognitive impairment observed in female patients may reflect their relatively high baseline abilities in the areas that are susceptible to PD, although the baseline MoCA score nor MMSE score were able to completely explain the association between sex and the development of cognitive impairment in the current data.

Several associations that were previously reported were not observed in the current analysis. RBD was reported to be more prevalent in males with PD than in females with PD,[9,10] although some studies have disagreed.[29,30] We were unable to confirm this association in the current longitudinal dataset. Although the prevalence of possible RBD, as detected by single-question screening was higher in male patients among the Fox Insight cohort, a similarly increased prevalence in possible RBD for non-PD male participants makes the PD-specific nature of this association questionable. Female PD patients were more depressed, according to previous reports.[11–14] We were not able to confirm a sex-associated difference in the presentation or progression of depression, in either the longitudinal data or the Fox Insight dataset. However, female PD patients expressed a depressive mood more frequently than male patients, in response to the related NMSQuest question ('feeling sad, 'low' or 'blue') from the Fox Insight dataset. However, the magnitude of the association was not different between PD and non-PD participants, indicating that the sex difference associated with this outcome may not be PD-specific. Regarding the NMSQ items evaluated, the similar null results except for NMSQ_Smell were reported previously in a cross-sectional analysis of de novo PD patients.[31] Regarding the discrepancy in NMSQ_Smell, it may be possible that the sex-difference in reported loss of smell/taste may be only detectable in the de novo PD stage.

The current study has some limitations. Fox Insight is an online-only cohort, which is inherently different from a clinic-based cohort; however, our analyses were mostly consistent across these two different settings. Additionally, because the study participants were almost all of European descent, the generalizability of these observations across different ancestrally distinct groups should be verified. In this study, we focused on the overall associations between sex and phenotypes and did not separate the biological mechanisms from the environmental mechanisms. For example , the effect of estrogen on PD has been investigated frequently and the conflicting results were reported.[32] but we did not collect necessary data to rigorously evaluate the impact of estrogen on the differences. Similarly, we did not have enough data to investigate environmental factors such as smoking, alcohol, diet, physical activity levels, and socio-economic factors. The different distribution of these factors by sex may explain the differences we observed in the current study. Well-designed studies are warranted to dissect the overall differences into each underlying pathway.

Despite some limitations, the current study has some strengths. First, the total number of participants examined in our longitudinal analysis was one of the largest populations studied. Second, although each study had different cohort characteristics, we controlled for heterogeneity and multiple comparisons to detect robust signals. Most of the associations identified between sex and disease presentation and progression were consistent between the longitudinal cohort and analyses performed using the independent Fox Insight dataset. Thus, our results could be generalized to PD patients across various disease stages in different contexts, given the range of studies incorporated. Third, by comparing PD patients with non-PD individuals, we obtained insight into whether sex-associated phenotypes in PD were disease-specific or reflected more general sex differences. Finally, female PD patients have been an underrepresented population in clinical trials.[33] The current work emphasizes the importance of recognizing gender biases when developing treatments for PD in the real world.

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Authors roles

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3. Manuscript Preparation: A. Writing of the first draft, B. Review and Critique;

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The study protocols were approved by the local institutional review boards and all the participants provided written (longitudinal studies) or online (Fox Insight) informed consent. 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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Figure legends

Figure 1: Forest plots depicting sex differences in outcomes in progression analyses

DATATOP, Deprenyl and Tocopherol Antioxidative Therapy of Parkinsonism; DIGPD, Drug Interaction with Genes in Parkinson's Disease; HBS, Harvard Biomarkers Study; NET-PD_LS1, NIH Exploratory Trials in Parkinson's Disease Large Simple Study 1; PARKFIT, ParkFit study; PARKWEST, The Norwegian ParkWest study; PDBP, Parkinson's Disease Biomarker Program; PICNICS, Parkinsonism Incidence and Cognitive and Non-motor heterogeneity In Cambridgeshire; PPMI, Parkinson's progression markers initiative; PreCEPT_PostCEPT, Parkinson Research Examination of CEP-1347 Trial and PostCEPT; PROPARK, Profiling Parkinson's disease study; and UDALL_PENN, Morris K. Udall Centers for Parkinson's Research.

P, non-adjusted p-values; I_sq, I^2 statistic; QEp, test of heterogeneity. "_scaled" scores were normalized (mean 0, standard deviation of 1) to the baseline distributions as the original scores.

Figure 2: Forest plots depicting sex differences in outcomes in baseline analyses

DATATOP, Deprenyl and Tocopherol Antioxidative Therapy of Parkinsonism; DIGPD, Drug Interaction with Genes in Parkinson's Disease; HBS, Harvard Biomarkers Study; NET-PD_LS1, NIH Exploratory Trials in Parkinson's Disease Large Simple Study 1; PARKFIT, ParkFit study; PARKWEST, The Norwegian ParkWest study; PDBP, Parkinson's Disease Biomarker Program; PICNICS, Parkinsonism Incidence and Cognitive and Non-motor heterogeneity In Cambridgeshire; PPMI, Parkinson's progression markers initiative; PreCEPT_PostCEPT, Parkinson Research Examination of CEP-1347 Trial and PostCEPT; PROPARK, Profiling Parkinson's disease study; and UDALL_PENN, Morris K. Udall Centers for Parkinson's Research.

P, non-adjusted p-values; I_sq, I^2 statistic; QEp, test of heterogeneity. "_scaled" scores were normalized (mean 0, standard deviation of 1) to the baseline distributions as the original scores.

Tables

Table 1. Baseline characteristics of study cohorts

Cohort	N	f-u, year	European %	Female, %	Stratum	Age, year old	Duration, y	LD, %	DA, %
PPMI	408	7.0	95.1	34.6	Male	62.15 (9.86)	0.53 (0.49)	-	-
					Female	60.76 (9.60)	0.60 (0.63)		
PreCEPT_PostCEPT	390	6.9	97.7	33.8	Male	59.83 (9.51)	0.79 (0.80)	-	-
					Female	60.96 (9.56)	0.84 (0.85)		
PARKWEST	181	5.0	100	37.8	Male	67.82 (9.21)	0.16 (0.10)	-	-
					Female	68.36 (9.10)	0.20 (0.14)*		
DATATOP	796	1.1	97.7	33.7	Male	61.45 (9.35)	1.16 (1.14)	-	-
					Female	60.34 (9.80)	1.10 (1.05)		
PICNICS	122	3.5	98.4	35.2	Male	67.85 (8.40)	0.30 (0.49)	30.4	17.7
					Female	67.93 (10.28)	0.12 (0.50)*	27.9	23.3
NET_PD_LS1	1705	4.0	92.7	35.7	Male	62.07 (9.32)	1.55 (1.08)	57.5	60.4
					Female	61.20 (10.06)	1.54 (1.10)	55.3	63.3
DIGPD	350	3.0	85.8	39.4	Male	61.45 (10.34)	2.55 (1.52)	65.6	77.8
					Female	62.40 (9.61)	2.46 (1.59)	62.3	63.0
PDBP	486	3.0	93.0	39.7	Male	65.03 (9.13)	5.31 (4.74)	81.9	50.2*
					Female	64.87 (8.67)	5.22 (4.78)	76.9	56.8
HBS	482	1.9	96.3	35.3	Male	65.79 (9.67)	4.28 (4.79)	73.7	39.4
					Female	66.60 (9.40)	3.97 (4.30)	70.0	42.4
PROPARK	327	5.0	NA	33.9	Male	59.56 (10.29)	6.48 (5.00)	67.1	69.9
					Female	59.51 (11.63)	6.98 (4.18)	64.0	79.3
PARKFIT	466	2.0	NA	33.3	Male	65.28 (7.41)	4.97 (4.25)	NA	NA
					Female	65.49 (7.60)	5.38 (4.76)		
UDALL_PENN	233	4.0	94.4	30.9	Male	70.53 (7.29)	5.73 (4.96)	84.5	46.0
					Female	70.14 (8.15)	6.64 (5.80)	90.3	56.9
Fox Insight (non-PD)	7588	-	95.8	78.8	Male	63.55 (7.89)	-	-	-
					Female	62.51 (7.39)*			
Fox Insight (PD)	17719	-	96.4	45	Male	66.72 (7.16)	4.61 (3.24)	80.3	29.4
					Female	66.00 (7.10)*	4.50 (3.25)*	76.8*	35.0*

f-u, median follow-up period; European, European descent; Duration, mean disease duration; LD, levedopa use; DA, dopamine agonist use. Age, mean (standard deviation). * $p<0.05$ for t-test comparing with male vs female.

DATATOP, Deprenyl and Tocopherol Antioxidative Therapy of Parkinsonism; DIGPD, Drug Interaction with Genes in Parkinson's Disease; HBS, Harvard Biomarkers Study; NET-PD_LS1, NIH Exploratory Trials in Parkinson's Disease Large Simple Study 1; PARKFIT, ParkFit study; PARKWEST, The Norwegian ParkWest study; PDBP, Parkinson's Disease Biomarker Program; PICNICS, Parkinsonism Incidence and Cognitive and Non-motor heterogeneity In Cambridgeshire; PPMI, Parkinson's progression markers initiative; PreCEPT_PostCEPT, Parkinson Research Examination of CEP-1347 Trial and PostCEPT; PROPARK, Profiling Parkinson's disease study; and UDALL_PENN, Morris K. Udall Centers for Parkinson's Research.

Table 2. Meta-analysis results for significant associations with sex and phenotypes (reference: male)

Outcome	Beta	SE	P	P-adj	Mean [95%CI]
Progression analysis					
Cognitive_Impairment	-0.436	0.102	2.1E-05	7.7E-4	0.65 [0.53, 0.79] (HR)
Dyskinesia	0.255	0.055	4.1E-06	1.6E-4	1.29 [1.16, 1.44] (HR)
UPDRS2_scaled	-0.139	0.029	1.1E-06	4.1E-5	-0.14 [-0.20, -0.08]
UPDRS_scaled	-0.113	0.025	5.3E-06	2.0E-4	-0.11 [-0.16, -0.06]
Baseline analysis					
Dyskinesia	0.434	0.129	7.3E-04	0.0277	1.54 [1.20, 1.99] (OR)
MoCA	0.634	0.186	6.8E-04	0.0251	0.63 [0.27, 1.00]
UPDRS2_scaled	-0.124	0.031	6.5E-05	0.0024	-0.12 [-0.18, -0.06]
UPDRS3_scaled	-0.114	0.031	2.5E-04	0.0093	-0.11 [-0.17, -0.05]
UPDRS_scaled	-0.107	0.027	6.9E-05	0.0026	-0.11 [-0.16, -0.05]

Progression analyses test the association between incidence rates (binomial) or rates of change per years (continuous) and sex. The models were adjusted for age and disease duration (both linear and square terms), indictors for levodopa and/or agonist usages. "_scaled" scores were normalized (mean 0, standard deviation of 1) to the baseline distributions as the original scores.
SE, standard error; P-adj, Bonferroni adjusted P (raw-P times 37 [the number of muliple-comparison]).
Mean [95%CI], Mean and 95% confidence interval of the difference in each scale. HR, hazard ratio; OR, Odds Ratio, UPDRS, unified Parkinson's disease rating scale; MoCA, Montreal Cognitive Assessment.

Table 3. Analysis results for sex difference in main term and interaction term with sex and disease duration in replication cohort (reference: male)

	PD								Control			
	Interaction term				Main term				Main term			
Outcome	Beta	SE	P	Consistency with LT analysis	Beta	SE	P	Consistency with LT analysis	Beta	SE	P	Test of Homogeneity in main effect
UPDRS2 total	-0.185	0.033	3.2E-08	Consistent	-0.487	0.184	8.1E-03	Consistent				
Cognitive IADL (PDAQ-15)	0.219	0.049	6.8E-06	Consistent	-0.024	0.266	0.928	Consistent	-0.668	0.297	0.025	0.106
Dyskinesia	0.073	0.032	0.024	Consistent	-0.311	0.205	0.129					
Wearing Off	-0.001	0.041	0.977	Consistent	0.259	0.217	0.232	Consistent				
Depression (GDS total >5)	-0.013	0.010	0.203	Consistent	-0.030	0.056	0.596	Consistent	-0.165	0.066	0.012	0.120
pRBD (single question)	-0.003	0.011	0.767	Consistent	-0.698	0.059	1.2E-32		-0.696	0.080	4.6E-18	0.990
NMSQ_Awake	0.001	0.012	0.963	Consistent	-0.216	0.072	2.5E-03		-0.292	0.091	1.3E-03	0.514
NMSQ_Sleep	-0.003	0.011	0.789	Consistent	0.406	0.058	2.4E-12		0.492	0.064	1.4E-14	0.317
NMSQ_Feel	-0.004	0.010	0.676	Consistent	0.384	0.055	4.3E-12		0.342	0.065	1.6E-07	0.628
NMSQ_Constipation	-0.018	0.010	0.072	Consistent	0.173	0.055	1.7E-03		0.310	0.075	3.8E-05	0.143
NMSQ_Smell	-0.011	0.011	0.314	Consistent	0.034	0.059	0.568	Consistent	-0.326	0.111	3.3E-03	4.2E-03

"Main term" is the average difference between the females and the males (reference: males). "Interaction term" is the interaction between disease duration and sex. The adjusted covariates were linear and square age for non-PD participants. For PD participants, linear and square disease duration, and indicators of levodopa and dopamine agonist usage were further adjusted.

SE, standard error; PDAQ-15, the Penn Parkinson's Daily Activities Questionnaire-15 (15-item measure of cognitive instrumental activities of daily living (IADL) for Parkinson's disease patients derived from the original 50-item PDAQ), ranging 0-60 (the lower the worse); Depression, Geriatric Depression Scale score more than 5. Consistency with longitudinal dataset analyses were evaluated for outcomes (Consistency with LT analysis).

NMSQ, Non Motor Symptom Questionnaire; NMSQ_awake: difficult to stay awake; NMSQ_Sleep, difficulty getting sleep at night; NMSQ_Feel, feeling sad, 'low' or 'blue'; NMSQ_Smell, loss or change in your ability to taste or smell.

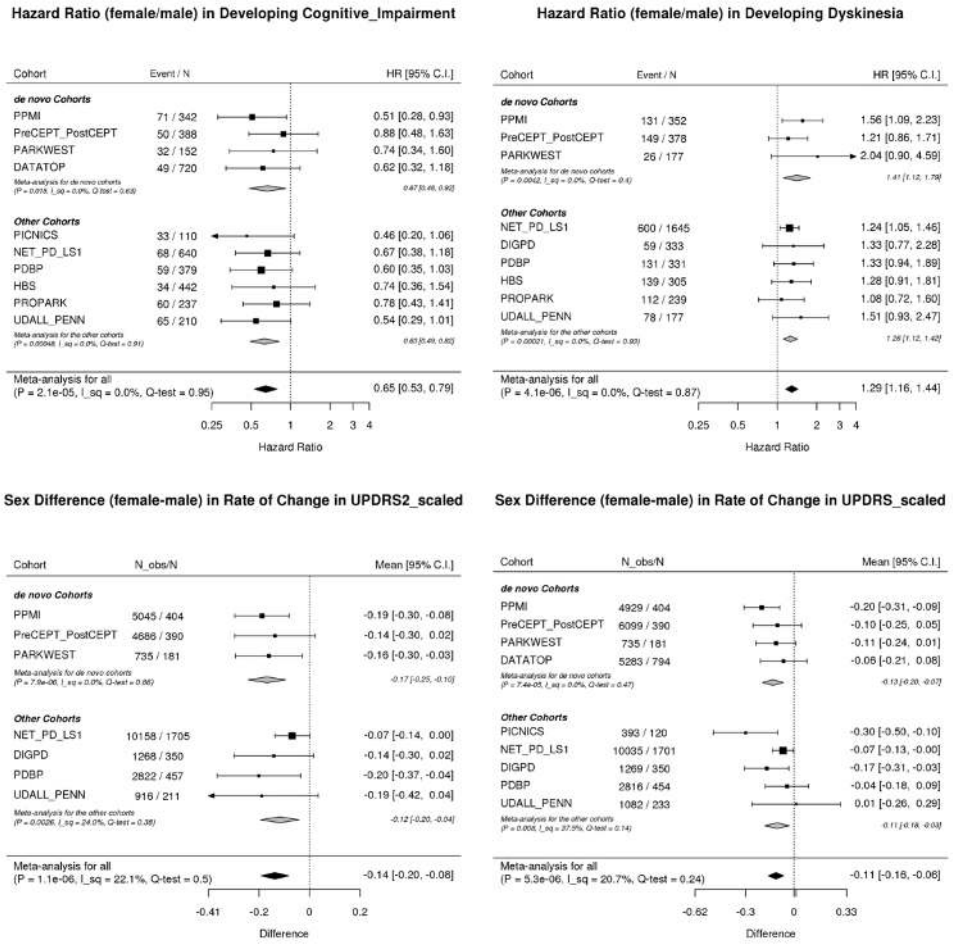

figure 1

152x152mm (300 x 300 DPI)

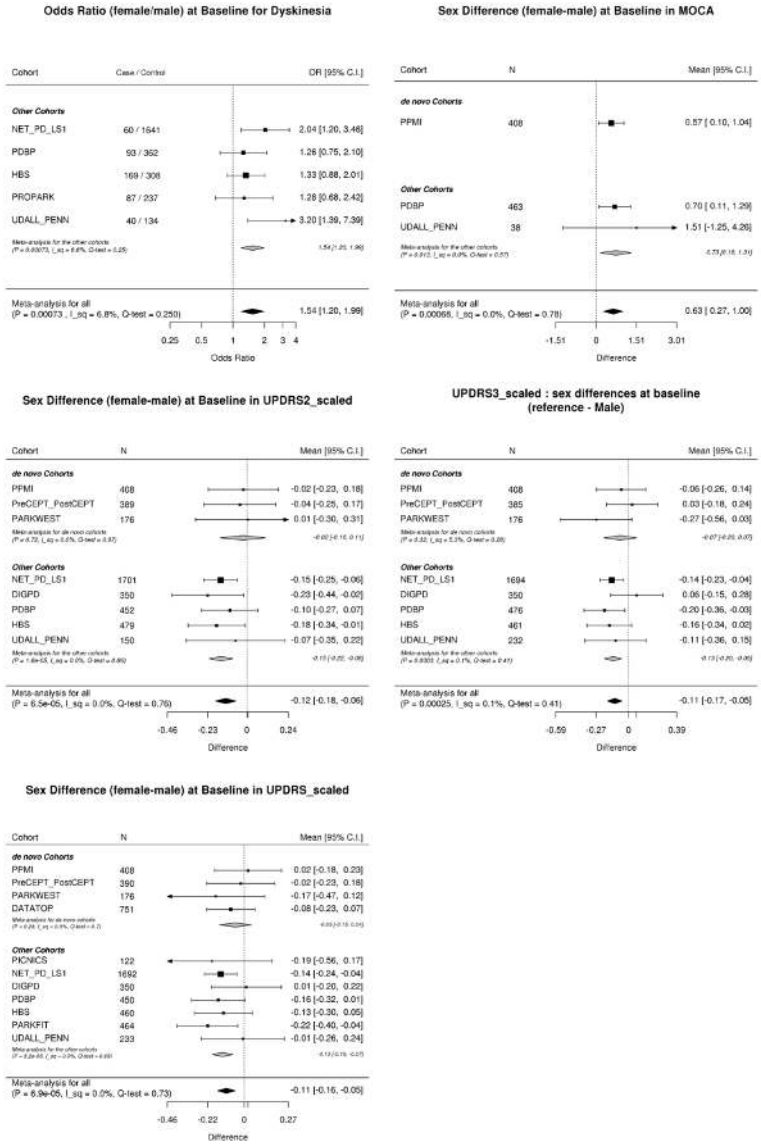

figure 2

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Differences in the presentation and progression of Parkinson's disease by sex

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Sex differences in Parkinson's disease

Abstract

Background: Previous studies reported various symptoms of Parkinson's disease (PD) associated with sex. Some were conflicting or confirmed only in one study.

Objectives: To examine sex associations to PD phenotypes cross-sectionally and longitudinally in large scale data.

Methods: We tested 40 clinical phenotypes, using longitudinal, clinic-based patient cohorts, consisting of 5,946 patients, with a median follow-up of 3.1 years. For continuous outcomes, we used linear regressions at baseline to test sex-associated differences in presentation, and linear mixed-effects models to test sex-associated differences in progression. For binomial outcomes, we used logistic regression models at baseline and Cox regression models for survival analyses. We adjusted for age, disease duration, and medication use. In the secondary analyses, data from 17,719 PD patients and 7,588 non-PD participants from an online-only, self-assessment PD cohort were cross-sectionally evaluated to determine whether the sex-associated differences identified in the primary analyses were consistent and unique to PD.

Results: Female PD patients had a higher risk of developing dyskinesia early during the follow-up period, with a slower progression in activities of daily living difficulties, and a lower risk of developing cognitive impairments compared with male patients. The findings in the longitudinal, clinic-based cohorts were mostly consistent with the results of the online-only cohort.

Conclusions: We observed sex-associated contributions to PD heterogeneity. These results highlight the necessity of future research to determine the underlying mechanisms and importance of personalized clinical management.

Keyword:

Parkinson's disease; gender; sex; dyskinesias; cognitive impairment; activities of daily livings;

Main text

Introduction

The prevalence of Parkinson's disease (PD) is 1.5–2.0 times higher in men than in women. This discrepancy suggests the potential existence of sex-associated factors that modify the disease process. Identifying the interplay between sex and PD has the potential to assist the development of disease-modifying therapy, inform patient management strategies, and allow the planning of more efficient clinical trials. Researchers have previously investigated sex-associated differences in phenotypes among patients with PD.[1–3] Male PD patients have been reported to present akinesia/rigid features,[4] cognitive impairment,[5–7] daytime sleepiness,[8] and rapid eye movement (REM) sleep behavioral disorder (RBD) more frequently than female PD patients.[9,10] In contrast, anxiety disorder/depression[11–14] and dyskinesia[11,15–17] were documented to occur more frequently in female PD patients than in male PD patients. However, these studies were generally small in sample size and predominantly performed in a cross-sectional setting.

In this study, we analyzed longitudinal data from 12 PD cohorts, representing 5,946 participants, with a median of 3.1 years of follow-up. This study had two objectives: (1) to identify the baseline differences between men and women, in terms of disease presentation, and (2) to identify the influences of sex on longitudinal symptom trajectory. Further, we analyzed the Fox Insight dataset, an online-only, PD research cohort, to assess whether the observations made using the longitudinal datasets were consistent in an independent dataset. Moreover, by analyzing the data from both PD participants and non-PD participants in the Fox Insight dataset, we were able to evaluate differences in the prevalence of self-reported outcomes between participants with and without PD. This analysis further illustrated that some of the identified differences may be influenced by general differences between males and females, whereas others are disease-specific.

Methods

Participants

12 longitudinal cohorts

We analyzed data from 12 longitudinal PD cohorts, from North America, Europe, and Australia, in this study (Table 1). Among these cohorts, the following four studies enrolled people with early-phase PD who were not being treated at the time of study enrollment (de novo cohorts): Parkinson's Progression Markers Initiative (PPMI), Parkinson Research Examination of CEP-1347 Trial study and its subsequent prospective study (PreCEPT/PostCEPT), the Norwegian ParkWest study (PARKWEST), and Deprenyl and Tocopherol Antioxidative Therapy of Parkinsonism (DATATOP). Other cohorts included Parkinsonism Incidence and Cognitive and Non-motor heterogeneity In Cambridgeshire (PICNICS), National Institutes of Health Exploratory Trials in Parkinson's Disease Large Simple Study 1 (NET_PD_LS1), Drug Interaction With Genes in Parkinson's Disease (DIGPD), Parkinson's Disease Biomarker Program (PDBP), Harvard Biomarkers Study (HBS), ParkFit Study (PARKFIT), Profiling Parkinson's Disease Study (PROPARK), and Udall Centers program (UDALL_PENN). Participants' information was obtained under appropriate written consent and with local institutional and ethical approval. The summary of the designs and inclusion/exclusion criteria applied to these cohorts are documented in the Supplemental Materials. The study protocols were approved at the local institutional review boards and the participants provided written informed consent.

Fox Insight

To evaluate the consistency of results from the longitudinal dataset, we explored an independent dataset, Fox Insight. Fox Insight is an online-only, PD research cohort.[18] The details of the study are available online (https://foxinsight.michaeljfox.org/). Individuals, aged 18 or older, with and without PD, were enrolled through in-person referral or online advertisements. The participants provided online informed consent, and self-reported demographic,

characteristics, symptoms, medical history, and PD medication data were collected. Although Fox Insight is a longitudinal study, we analyzed the data cross-sectionally for the present study because the follow-up periods were relatively short (e.g., the median follow-up period was 0.4 years for Non-Motor Symptoms Questionnaire). During the analysis step, we adjusted for age and disease duration. To limit the impacts of the extreme data points, we included participants from the middle 80% of the age distribution and the disease duration distribution (only among PD participants), which excluded any participants younger than the lower 10th percentile (< 46.8 years old) or older than the 90th percentile (> 77.4 years old) and PD patients with a disease duration shorter than one year (10th percentile) and longer than 13.5 years (90th percentile).

Measurements

Clinical Data Harmonization Among the 12 cohorts

Twenty-three measurements, 11 binomial and nine continuous measurements, were analyzed as outcome measures. Binomial outcomes included constipation, mild cognitive impairment, depression, daytime sleepiness, hyposmia, insomnia, wearing off, dyskinesias, RBD, restless-leg syndrome, and modified Schwab and England Activities of Daily Living Scale scores of 70 or lower (SEADL70). Some binomial outcomes had study-specific outcomes, and these criteria are summarized in the Supplemental Materials. For continuous outcomes, we collected the Hoehn and Yahr (HY) stage scale, total and sub-scores for the Unified Parkinson's Disease Rating Scale (UPDRS) or the Movement Disorder Society–revised version (MDS-UPDRS), Mini-Mental State Examination, Montreal Cognitive Assessment (MoCA), and modified Schwab and England Activities of Daily Living Scale (SEADL). UPDRS scores were normalized to the z-values (UPDRS*_scaled).

Fox Insight

The February 2020 data was downloaded from https://foxden.michaeljfox.org. The demographic and disease status data were obtained from enrollment and registration questionnaires. For clinical outcomes of interest, we obtained the responses from the following questionnaires: Geriatric Depression Scale (GDS) for depression (score of six or higher);[19] Non-Motor Symptoms Questionnaire (NMS-QUEST) for constipation, depressed mood (Mood depressed) and a proxy for lack of the sense of smell/taste;[20] MDS-UPDRS Part II questionnaire; REM Sleep Behavior Disorder Single-Question Screen;[21] 15-item Penn Parkinson's Disease Daily Activities Questionnaire (PDAQ-15) for cognition-related instrumental functional abilities;[22] and Understanding the Impact of Off and On in Parkinson's Patients Questionnaire for dyskinesia and wearing off.

Statistical analysis

Linear and logistic models were used to analyze baseline differences in PD presentation between male and female patients, per cohort. For binomial outcomes, a minimum of 25 outcomes should be observed in the analyzed cohort. Covariates were the linear and square terms of age and disease duration, to adjust for linear and non-linear effects. In addition, we adjusted for levodopa and dopamine agonist use. To test differences in the progression rates among continuous outcomes, we used linear mixed-effects models, with the same covariates as the baseline models and random effects on the individual intercept and slope (change per year). We evaluated sex-associated differences in progression rates by testing the interaction between sex and disease duration. Survival analyses were conducted among those who did not have an outcome at baseline. Cox regression models were used, adjusting for the same covariates as those used in the baseline models. Any outcomes with fewer than 20 events over the follow-up period were not analyzed. The R model statements for these analyses are summarized in the Supplemental Materials.

Then, we combined the cohort-level results with an inverse variance-weighted random-effect model. We focused on robust associations throughout the cohorts; therefore, meta-analyses with p-values less than 0.05 for a test of homogeneity

were excluded from further evaluations. Any associations with a two-sided p-value of 0.05, after Bonferroni-correction for the number of total analyses, were considered significant.

For the analysis of the Fox Insight dataset, we tested two terms: the mean difference between males and females (main term) and the interaction between sex and disease duration (interaction term). The adjusted covariates were linear and square age, linear and square disease duration, and indicators of levodopa and dopamine agonist usage. We further analyzed the association between sex and outcomes among non-PD participants, adjusted for linear and square age. Then, we conducted a test of homogeneity between sex-associated differences identified among PD cases and non-PD participants, to evaluate whether the sex differences were PD-specific or reflected differences observed in the non-PD population. In the analyses for this dataset, we used a significance level of 0.05 for the raw p-value because the purpose of these analyses was to evaluate consistency with the longitudinal analyses.

All the statistical analyses and drawings were executed using R version 3.6 and python version 3.7. The analysis scripts are available at https://github.com/neurogenetics/PDpheno_by_sex.

Results

The cohort participants are summarized in Table 1. Participants in these cohorts varied in age and PD stage; however, most participants were in relatively early PD phases. The majority of participants were of European descent. Fox Insight included more female participants than the other cohorts, and the ratio of females to males was especially high among non-PD participants, as previously described.[23] Moreover, we did not observe a significant difference in age of diagnosis between the men and the women among each cohort except for Fox Insight, in which the female patients had on average 0.61 (SD: 0.12) years younger age of diagnosis than the male patients. Interestingly, the age of non-PD participants in Fox Insight was also younger than male non-PD participants. The younger age of onset may be reflecting different age distributions of the study population by sex in Fox Insight. In the following analyses, we adjusted for age, disease duration and medications.

In total, we conducted 40 meta-analyses, using the clinic-based longitudinal data, ~~two~~ three of which were rejected following a test of heterogeneity, with a significance level of 0.05. Using the Bonferroni correction of multiple comparisons, we set our p-value (P) threshold to 0.05/3~~7~~8 =0.0013~~5~~2. Among these associations, nine were significant, and the direction and magnitude of associations linked to being female compared with being male are shown in Table 2 and Figure 1/2. (All meta-analysis results can be found in Supplemental Materials).

Female PD patients were less likely to develop cognitive impairments over time {hazard ratio (HR) 0.65 [0.53, 0.79] ~~0.70 [0.59, 0.83]~~ (mean [95% confidence interval]), P = 2.1~~4.8~~E-5} than male PD patients, and an even stronger association was observed when we adjusted for years of education (HR 0.59 [0.48, 0.73], P = 4.6E-7, ~~0.63 [0.53, 0.76], P = 4.3E-7,~~ Supplemental Material). This association remain significant when we further adjusted for the baseline MoCA score (HR 0.56 [0.37, 0.86], P = 0.007) or the baseline MMSE score (HR 0.67 [0.51, 0.90], P = 0.007, Supplemental Material) at the significance level of 0.05. Additionally, the baseline MoCA scores were higher in female patients (0.63 [0.27, 1.00]) than in male patients, whereas the baseline MMSE score was not significantly different between sexes (P = 0.97, Supplemental Materials).

Female patients presented with a higher rate of developing dyskinesia (HR 1.29 [1.16, 1.44]). To assess the impacts of weight, body mass index (BMI) and medication on this association, we conducted ad hoc analyses on a subset of data (PDBP, PPMI, and NET_PD_LS1: 2,281 participants) for which height at baseline, weight at baseline, and medication at visits were recorded. We adjusted the analyses for each of these factors. With the "weight" adjustment, the association was no longer significant (P = 0.058), whereas the magnitude of the association became larger when adjusted for levodopa dosages or levodopa equivalent dosages. Adjusting for BMI did not substantially change the magnitude of the association (Beta: from 0.284 to 0.249), and the sex difference remained still significant (Supplemental Materials). Consistent with the higher incidence rate of dyskinesia in female patients, female PD patients in non-de novo cohorts also presented more dyskinesia at baseline than male patients.

Activities of daily living (ADL), captured in the UPDRS Part II, were better in female PD patients than in male PD patients in the baseline analysis (-0.12 [-0.18, -0.06], in the z-score), and the progression rate was slower in female patients than in male patients (-0.14 [-0.20, -0.08] in z-score per year). We added post-hoc analyses of UPDRS Part II scores in the different versions separately. The baseline score differences (female-male) were -0.57 [-1.20, 0.06] (P = 0.07) in MDS-UPDRS and -0.52 [-0.82, -0.21] (P = 7.9E-4) in the original UPDRS. The differences in the progression rate were -0.81 [-1.18, -044] (P = 1.4E-5) in MDS-UPDRS and -0.43 [-0.71, -0.15] (P = 2.5E-3) in the original UPDRS. A more detailed analysis of the forest plots of the UPDRS Part II scores at baseline showed that the associations between sex and UPDRS Part II were not apparent among the de novo cohorts but, rather, were driven by differences observed in the non-de novo cohorts (Figure 1). Although we did not find significant sex-associated differences in progression rates in the UPDRS Parts I/III/IV, the rate of change for the total UPDRS scores was significantly milder in female patients than in male patients (-0.11 [-0.16, -0.06] per year, in the z-score). In the raw scores, the sex-associated difference (female-male) in rate of change in MDS-UPDRS total score (female-male) was -2.7 [-3.47, -1.95] (P = 2.3E -12) and that of the original UPDRS total score was -0.91 [-1.33, -0.49], (P = 2.66E-05). When only considering the de novo cohorts, similar results were reported for UPDRS part III, with a slower progression rate in female patients than in male patients (-0.14 [-0.21, -0.07] in z-score per year, P = 2.6E-5, Supplemental Materials). This was corresponding to -1.59 [-2.47, -0.71] (P = 4.6E-4) per year difference (female-male) in the rate of change in MDS-UPDRS Part III or -1.01 [-1.78, -0.24] (P = 0.01) per year in the original UPDRS Part III.

Finally, female patients also had lower scores on the UPDRS Part III and the UPDRS total score compared with male patients during the baseline analyses.

When analyzing similar phenotypes within the Fox Insight dataset, we generally confirmed the results of the longitudinal dataset analyses (Table 3). In the Fox Insight dataset analysis, the interaction terms between sex and disease duration indicated the average sex-associated differences in the longitudinal trajectories for the outcomes. For example, a positive association for the interaction between disease duration and PDAQ-15 indicated that the PDAQ-15 scores for female patients were higher than those in male patients (i.e., better cognition-related instrumental functional abilities) among

patients with longer disease durations in the Fox Insight dataset. To illustrate this, we visualized the sex differences, stratified by disease duration (Supplemental Materials). The results are consistent with those for the longitudinal dataset analysis, indicating that female patients had a lower risk of developing cognitive impairments during the disease course. Similarly, the results from the Fox Insight dataset were consistent with the increased rate of dyskinesia development among female patients compared with male patients, and the lower scores and a slower deterioration rate in UPDRS Part II among female patients, as observed in the longitudinal analyses.

In addition, null differences between male and female patients in the presentation and progression of wearing off, depression, and hyposmia were also supported by the Fox Insight dataset. In contrast, the loss of the sense of smell/taste was significantly more frequently reported in males among the control participants. Having PD might diminish the general sex difference associated with this phenotype.

Single question answers for RBD and some NMSQuest questionnaire questions regarding “difficult to stay awake” (NMSQ_Awake), “difficulty in getting to sleep” (NMSQ_Sleep), “feeling sad, low or blue” (NMSQ_Feel), and NMSQ_Constipation were significantly different according to sex in the Fox Insight dataset. The prevalences of similar outcomes, such as possible RBD, daytime sleepiness, insomnia, depression, and constipation, were not significantly associated with sex in the meta-analyses of 12 longitudinal cohorts. However, the test for these associations gives raw p-values less than 0.05, with the same directions as the Fox Insight results. The primary analyses may not have included large enough sample sizes to detect these associations. All of the sex-phenotype associations among PD participants, not significant in the longitudinal dataset but significant in the Fox Insight dataset, were also significant among non-PD participants. In addition, based on the test of homogeneity between the results from PD and non-PD participants, suggesting that the magnitudes of these sex-associated differences in PD participants did not differ from those in non-PD participants.

Discussion

We analyzed clinic-based, longitudinal data from 5,946 participants and meta-analyzed the differences in presentation and progression of phenotypes between men and women with PD. We also used web-based, online cohorts and analyzed data from 17,719 PD patients and 7,588 non-PD participants to confirm our results. The results suggested that female PD patients develop dyskinesia early, progress more slowly with respect to ADL restrictions, and are less likely to develop cognitive impairments. For some non-motor symptoms explored in the online questionnaires (such as possible RBD, daytime sleepiness, insomnia, depressive mood, and constipation), we found significant sex-associated differences among PD participants, only in the Fox Insight dataset. These unconfirmed sex-associated differences may not be specific to PD, as we also observed the same associations in the non-PD participants.

Some studies have previously reported that female patients demonstrated an increased risk of developing earlier and more severe dyskinesia[11,15] and a longer duration of dyskinesia.[16] These reports are consistent with the faster development of dyskinesia among female patients and the large rate of UPDRS Part IV score increases observed in our study. The reasons for this phenomenon are not fully understood, but the relatively higher levodopa dosages with respect to body weight in females may be partially responsible.[17] For example, the commonly used levodopa tablet contains 50 mg or 100 mg levodopa and this is relatively a larger jump for those with less weight, and that may result in stronger treatment for them compared with those with more weight. Our ad hoc analyses also suggested that body weight plays a role in the association between sex and the early development of dyskinesia.

Contradictory results have been reported previously with regards to sex-associated differences in ADL impacts. Two studies evaluated patients who underwent surgical treatment for PD. One study observed no differences in the UPDRS Part II scores between males and females, whereas the other study reported that females had worse scores than males. In these studies, females had a longer duration of disease, which may have affected the results. Another cross-sectional study also reported worse UPDRS Part II scores among female patients.[11] They reported that, among the five categories of overall ADL capacity, the two most-severe categories were more frequent among females than males, based on the results

of a chi-squared test, whereas our analyses used UPDRS Part II scores and multivariable regression models. These different outcome measurements and statistical approaches may account for different results.

The slower development of cognitive declines in female patients was reported by some longitudinal studies.[5,6,24] The executive and attention features were primarily affected in PD patients. While Alzheimer's disease, for which women confer more risk, is emphasized as disability in the memory feature, the executive and attention features are primarily affected in PD patients. MoCA is more sensitive for detecting dysfunctions in these areas than MMSE,~~We observed discrepancies between MoCA and MMSE scores in the baseline analyses, which may derive from the MoCA being more sensitive for the detection of executive dysfunction than the MMSE.~~[25] and this may be one of the reasons that we observed baseline difference in MoCA but not MMSE. In contrast, the longitudinal differences in the rates of decline for either the MoCA or MMSE were not significantly different between the two sexes, in our data. Interestingly, MoCA scores were sometimes reported to be higher in healthy aging women than in men.[26–28] The slower development of cognitive impairment observed in female patients may reflect their relatively high baseline abilities in the areas that are susceptible to PD, although the baseline MoCA score nor MMSE score were able to completely explain the association between sex and the development of cognitive impairment in the current data.

Several associations that were previously reported were not observed in the current analysis. RBD was reported to be more prevalent in males with PD than in females with PD,[9,10] although some studies have disagreed.[29,30] We were unable to confirm this association in the current longitudinal dataset. Although the prevalence of possible RBD, as detected by single-question screening was higher in male patients among the Fox Insight cohort, a similarly increased prevalence in possible RBD for non-PD male participants makes the PD-specific nature of this association questionable. Female PD patients were more depressed, according to previous reports.[11–14] We were not able to confirm a sex-associated difference in the presentation or progression of depression, in either the longitudinal data or the Fox Insight dataset. However, female PD patients expressed a depressive mood more frequently than male patients, in response to the related NMSQuest question ('feeling sad, 'low' or 'blue') from the Fox Insight dataset. However, the magnitude of the association was not different between PD and non-PD participants, indicating that the sex difference associated with this outcome may not be PD-specific. Regarding the NMSQ items evaluated, the similar null results except for NMSQ_Smell were reported

previously in a cross-sectional analysis of de novo PD patients.[31] Regarding the discrepancy in NMSQ_Smell, it may be possible that the sex-difference in reported loss of smell/taste may be only detectable in the de novo PD stage.

The current study has some limitations. Fox Insight is an online-only cohort, which is inherently different from a clinic-based cohort; however, our analyses were mostly consistent across these two different settings. Additionally, because the study participants were almost all of European descent, the generalizability of these observations across different ancestrally distinct groups should be verified. In this study, we focused on the overall associations between sex and phenotypes and did not separate the biological mechanisms from the environmental mechanisms. For example , the effect of estrogen on PD has been investigated frequently and the conflicting results were reported.[32] but we did not collect necessary data to rigorously evaluate the impact of estrogen on the differences. Similarly, we did not have enough data to investigate environmental factors such as smoking, alcohol, diet, physical activity levels, and socio-economic factors. The different distribution of these factors by sex may explain the differences we observed in the current study. Well-designed studies are warranted to dissect the overall differences into each underlying pathway.~~We believe that it will be important to examine the potential effects of environmental factors, such as estrogen usage, history of pregnancy, tobacco use, and pesticide exposure, which may contribute to the differences between male and female PD patients.~~

Despite some limitations, the current study has some strengths. First, the total number of participants examined in our longitudinal analysis was one of the largest populations studied. Second, although each study had different cohort characteristics, we controlled for heterogeneity and multiple comparisons to detect robust signals. Most of the associations identified between sex and disease presentation and progression were consistent between the longitudinal cohort and analyses performed using the independent Fox Insight dataset. Thus, our results could be generalized to PD patients across various disease stages in different contexts, given the range of studies incorporated. Third, by comparing PD patients with non-PD individuals, we obtained insight into whether sex-associated phenotypes in PD were disease-specific or reflected more general sex differences. Finally, female PD patients have been an underrepresented population in clinical trials.[33] The current work emphasizes the importance of recognizing gender biases when developing treatments for PD in the real world.

~~In conclusion, we observed that female PD patients developed dyskinesias earlier in their disease course, and progressed more slowly, with respect to cognitive deficits and ADL problems compared with male PD patients. The associations were generally consistent across the different longitudinal cohorts and the online survey.~~

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Authors 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;

HI: 1A,1C,2A,2B,3A, CB: 1A,1B,2B,3B, MBM: 1B,3B, HLL: 1B,3B, JJK: 1B,3B, GL: 1A,1B,3B, JMG: 1A,1B,3B, JCC: 1A,1B,3B, LP: 1A,1B,3B, MN: 1A,1B,3B, LS: 1A,1B,3B, NA: 1A,1B,3B, SJH: 1A,1B,3B, MF: 1A,1B,3B, KDHN: 1A,1B,3B, JR: 1A,1B,3B, SE: 1A,1B,3B, FF: 1A,1B,3B, PA: 1A,1B,3B, KMS: 1A,1B,3B, RW: 1A,1B,3B, VMD: 1A,1B,3B, DGH: 1A,1B,3B, JRG: 1A,1B,3B, AGDW: 1A,1B,3B, AB: 1A,1B,3B, GA: 1A,1B,3B, AJN: 1A,1B,3B, OBT: 1A,1B,3B, JRE: 1A,1B,3B, DPB: 1A,1B,3B, KE: 1A,1B,3B, CEW: 1A,1B,3B, FD: 1A,1B,3B, DKS: 1A,1B,3B, OA: 1A,1B,3B, BR: 1A,1B,3B, MT: 1A,1B,3B, PH: 1A,1B,3B, BRB: 1A,1B,3B, DW: 1A,1B,3B, RAB: 1A,1B,3B, CHWG: 1A,1B,3B, BPW: 1A,1B,3B, JJH: 1A,1B,3B, CRS: 1A,1B,3B, ABS: 1A,1B,3B, MAN: 1A,1B,2C,3B.

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Ethical compliance Statement

The study protocols were approved by the local institutional review boards and all the participants provided written (longitudinal studies) or online (Fox Insight) informed consent. 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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Figure legends

Figure 1: Forest plots depicting sex differences in outcomes in progression analyses

DATATOP, Deprenyl and Tocopherol Antioxidative Therapy of Parkinsonism; DIGPD, Drug Interaction with Genes in Parkinson's Disease; HBS, Harvard Biomarkers Study; NET-PD_LS1, NIH Exploratory Trials in Parkinson's Disease Large Simple Study 1; PARKFIT, ParkFit study; PARKWEST, The Norwegian ParkWest study; PDBP, Parkinson's Disease Biomarker Program; PICNICS, Parkinsonism Incidence and Cognitive and Non-motor heterogeneity In Cambridgeshire; PPMI, Parkinson's progression markers initiative; PreCEPT_PostCEPT, Parkinson Research Examination of CEP-1347 Trial and PostCEPT; PROPARK, Profiling Parkinson's disease study; and UDALL_PENN, Morris K. Udall Centers for Parkinson's Research.

P, non-adjusted p-values; I_sq, I^2 statistic; QEp, test of heterogeneity. "_scaled" scores were normalized (mean 0, standard deviation of 1) to the baseline distributions as the original scores.

Figure 2: Forest plots depicting sex differences in outcomes in baseline analyses

DATATOP, Deprenyl and Tocopherol Antioxidative Therapy of Parkinsonism; DIGPD, Drug Interaction with Genes in Parkinson's Disease; HBS, Harvard Biomarkers Study; NET-PD_LS1, NIH Exploratory Trials in Parkinson's Disease Large Simple Study 1; PARKFIT, ParkFit study; PARKWEST, The Norwegian ParkWest study; PDBP, Parkinson's Disease Biomarker Program; PICNICS, Parkinsonism Incidence and Cognitive and Non-motor heterogeneity In Cambridgeshire; PPMI, Parkinson's progression markers initiative; PreCEPT_PostCEPT, Parkinson Research Examination of CEP-1347 Trial and PostCEPT; PROPARK, Profiling Parkinson's disease study; and UDALL_PENN, Morris K. Udall Centers for Parkinson's Research.

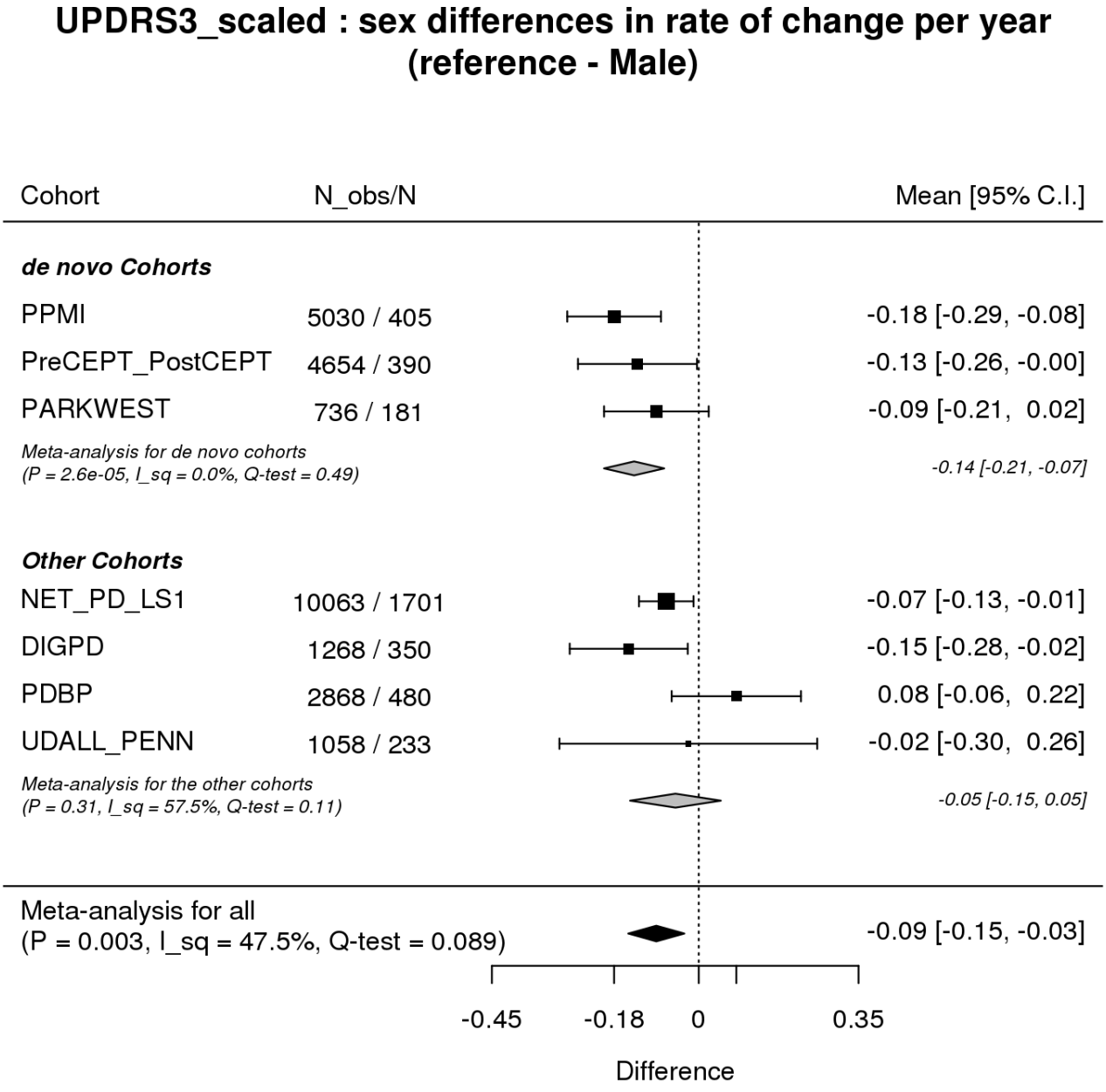
P, non-adjusted p-values; I_sq, I^2 statistic; QEp, test of heterogeneity. "_scaled" scores were normalized (mean 0, standard deviation of 1) to the baseline distributions as the original scores.

Supplemental Materials

Table of Contents

Supplemental Figures

Forest plots for the sex differences in rate of change in UPDRS part III



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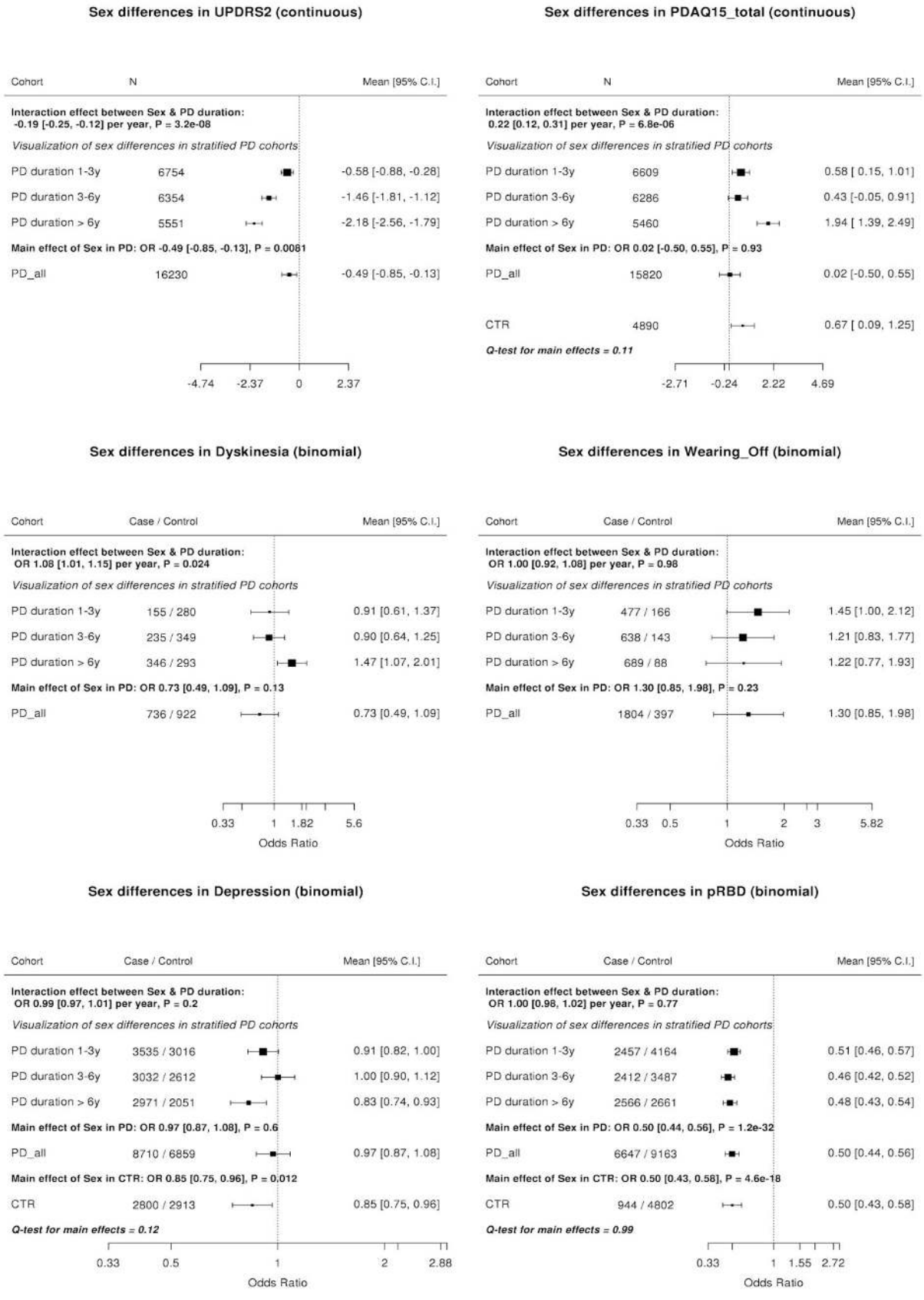

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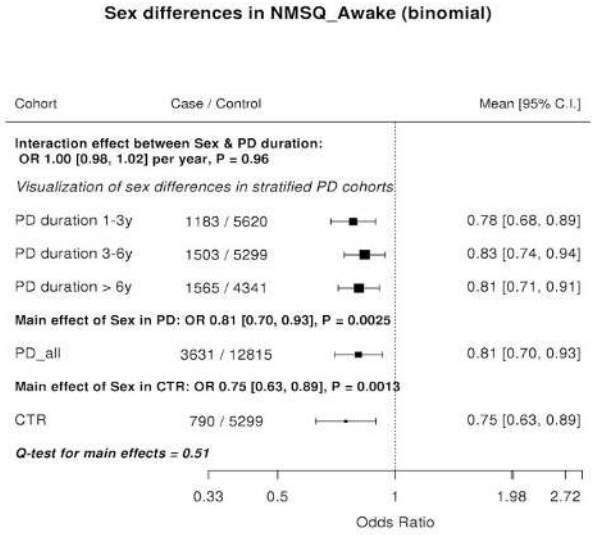
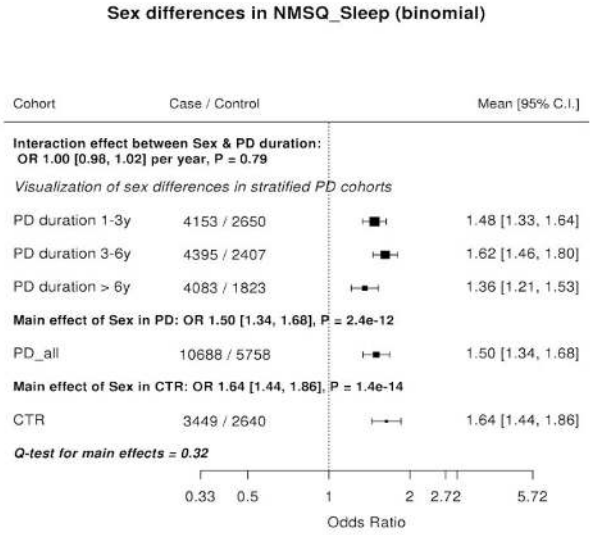
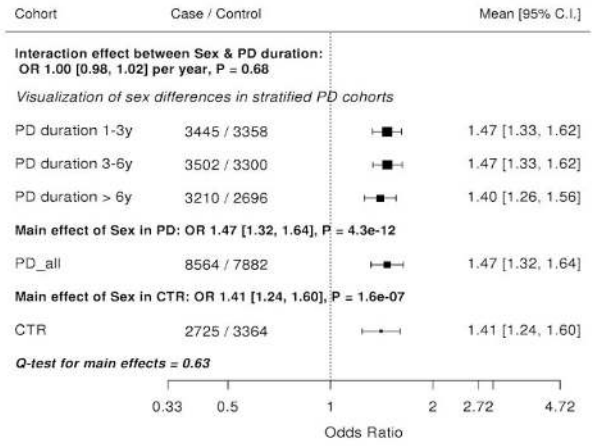
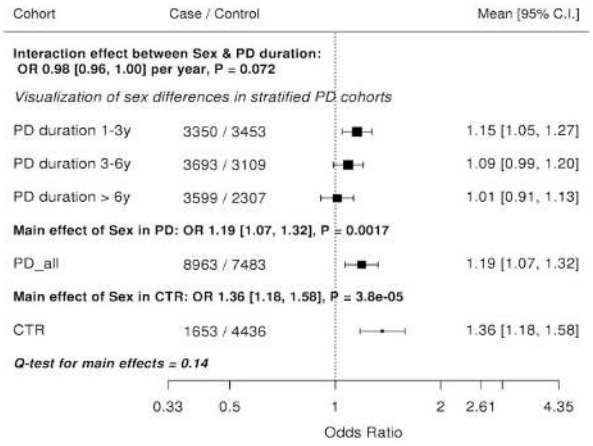
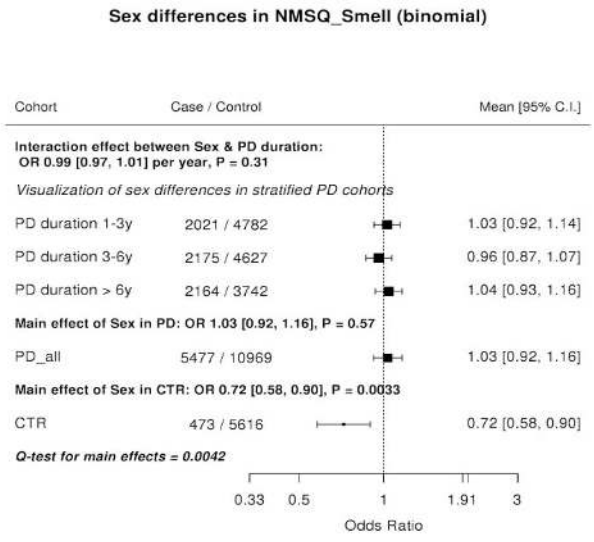


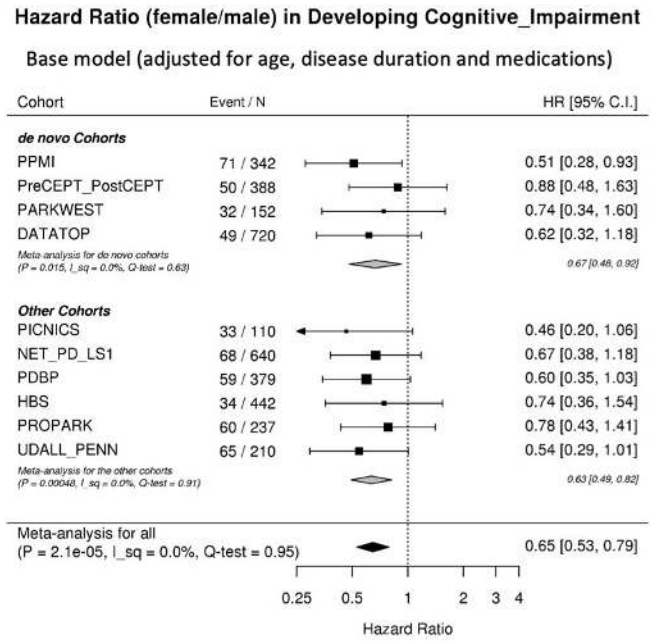


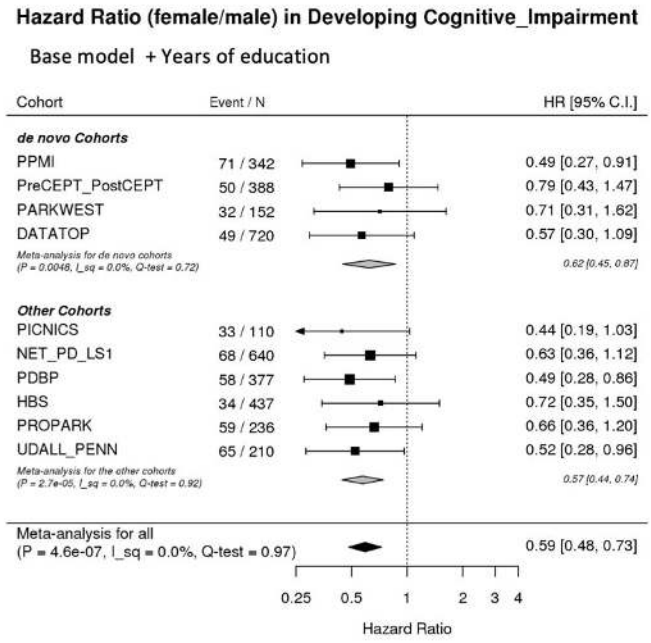


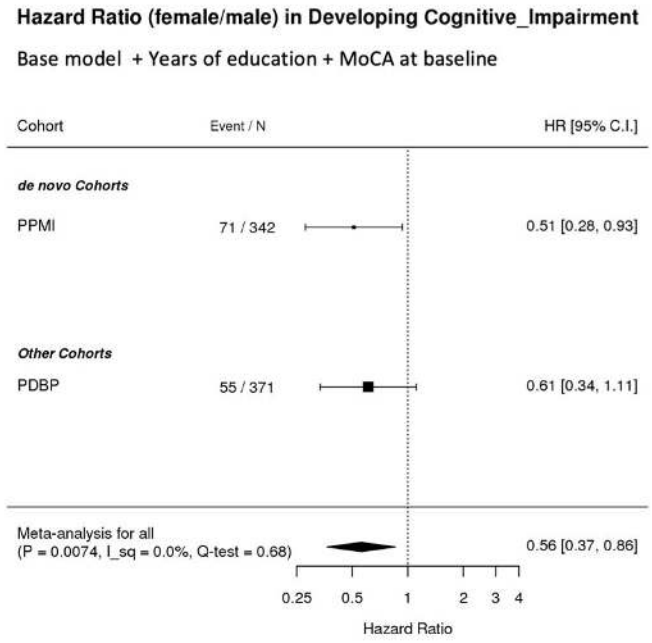


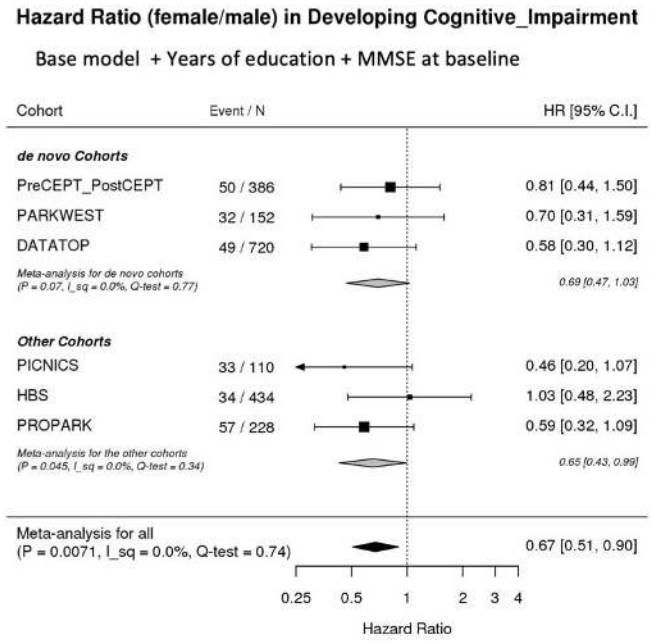


Sex differences in developing cognitive impairment further adjusted for years of education and baseline cognitive test results.









Supplemental Tables

See the next page

Cohort specific definitions of binomial outcomes

Supplemental Table. Cohort specific definitions of binomial outcomes

	DATATOP	DIGPD	HBS	NET-PD_LS1	ParkFit	ParkWest	PDBP	PICNICS	PPMI	PreCEPT/ PostCEPT	ProPark	Udall
Hyposmia	-	-	-	-	-		UPSIT≦p15	-	UPSIT≦p15	UPSIT≦p15		UPSIT≦p15
Cognitive Impairment	MMSE<27	-	MMSE<27	SCOPA_COG<25	MMSE<27	MMSE<27	MoCA<24	MMSE<27	MoCA<24	MMSE<27	MMSE <27	MoCA<24
Wearing off	-	Neurologist diagnosis	any>0 in UPDRS Q36-Q39	UPDRS4 Q39>0	-	UPDRS4 Q39>0	MDS-UPDRS4.3>0	MDS-UPDRS4.3>0	MDS-UPDRS4.3>0	MDS-UPDRS4.3>0	SPES/SCOPA item 20 >0	MDS-UPDRS4.3>0
dyskinesia	AE report	Neurologist diagnosis	any>0 in UPDRS Q32-Q35>0 at any of them	UPDRS4 Q32>0	-	UPDRS4 Q32>0	MDS-UPDRS4 .1>0	MDS-UPDRS4 .1>0	MDS-UPDRS4 .1>0	MDS-UPDRS4 .1>0	SPES/SCOPA item 18 >0	MDS-UPDRS4 .1>0
depression	AE report	Neurologist diagnosis	GDS15 >5	BDI>14	-	UPDRS Q3≧2	HDRS>9	BDI>14 or GDS15>5	GDS15 >5	UPDRS Q3 >0	BDI>14	GDS15>4
restless legs syndrome	-	RLS criteria	Medical history	-	-	-	MSQ3 yes	-	RBDSQ, RLS yes	-	-	-
Constipation	AE report	NMSQuest, Q5 yes	-	-	-	-	MDS-UPDRS1.11>0	MDS-UPDRS1.11>0	MDS-UPDRS1.11>0	MDS-UPDRS1.11>0	SCOPA-AUT item 5>0	-
pRBD	-	-	-	-	-	RBDSQ>5	MSQ1 yes	-	RBDSQ>5	-	--	-
Daytime sleepiness	AE report	Neurologist diagnosis	-	-	-	Epworth > 9	Epworth > 9	ESS>9 OR MDS-UPDRS1.8>2	Epworth > 9	MDS-UPDRS1.8>0	SCOPA-SLEEP daytime sleepiness (section D) >4	-
Insomnia	AE report	Neurologist diagnosis	UPDRS Q41>0	-	-	"Do you have problems sleeping?" Yes	UPDRS Q41>0	MDS-UPDRS1.7>0	MDS-UPDRS1.7>0	MDS-UPDRS1.7>0	SCOPA-SLEEP Nighttime (section B) >6	-

BDI, Beck's Depression Inventory; GDS, Geriatric Depression Scale; HDRS, Hamilton Depression Rating Scale; MMSE, the Mini-Mental State Examination; MoCA Montreal Cognitive Assessment; MSQ, Mayo Sleep Questionnaire; NMS, Non-motor Symptoms Questionnaire; RBD, REM sleep Behavior Disorder; UPDRS Unified Parkinson's Disease Rating Scale (original); MDS-UPDRS, Movement disorder society revised UPDRS version; UPSIT, The University of Pennsylvania Smell Identification Test, 15 percentile (p15) were determined by the sex/age table described in the manual.
Cutoff scores for cognitive impairment were derived from Neurology. 2010 Nov 9;75(19):1717-25. doi: 10.1212/WNL.0b013e3181fc29c9; AE report, report of the symptom as an adverse event during the study;

All meta-analysis results

Supplemental Table. All meta-analysis results

Outcome	Model	Beta	SE	P	Qep	P-adj	Mean [95%CI]
UPDRS2_scaled	mixed	-0.139	0.029	1.1E-06	0.50	4.1E-05	-0.139 [-0.195, -0.083]
Dyskinesia	survival	0.256	0.055	4.1E-06	0.87	1.5E-04	1.291 [1.158, 1.439] (HR)
UPDRS_scaled	mixed	-0.113	0.025	5.3E-06	0.24	2.0E-04	-0.113 [-0.161, -0.064]
Cognitive_Impairment	survival	-0.436	0.102	2.1E-05	0.95	7.7E-04	0.647 [0.529, 0.790] (HR)
UPDRS2_scaled	linear	-0.124	0.031	6.5E-05	0.76	2.4E-03	-0.124 [-0.185, -0.063]
UPDRS_scaled	linear	-0.107	0.027	6.9E-05	0.73	2.6E-03	-0.107 [-0.160, -0.054]
UPDRS3_scaled	linear	-0.114	0.031	2.5E-04	0.41	9.3E-03	-0.114 [-0.175, -0.053]
MoCA	linear	0.634	0.186	6.8E-04	0.78	0.025	0.634 [0.268, 0.999]
Dyskinesia	logistic	0.434	0.129	7.3E-04	0.25	0.027	1.544 [1.200, 1.986] (OR)
UPDRS3_scaled	mixed	-0.092	0.031	3.0E-03	0.09	0.111	-0.092 [-0.153, -0.031]
Daytime_Sleepiness	survival	-0.276	0.095	3.6E-03	0.79	0.132	0.759 [0.630, 0.914] (HR)
UPDRS4_scaled	linear	0.103	0.037	4.8E-03	0.21	0.178	0.103 [0.032, 0.175]
RSL	survival	0.357	0.137	9.2E-03	0.57	0.342	1.429 [1.092, 1.871] (HR)
Insomnia	logistic	0.243	0.096	0.011	0.56	0.413	1.275 [1.057, 1.539] (OR)
MoCA	mixed	0.257	0.102	0.012	0.87	0.429	0.257 [0.057, 0.456]
Constipation	survival	0.227	0.092	0.013	0.48	0.490	1.255 [1.049, 1.503] (HR)
Depression	logistic	0.215	0.087	0.014	0.79	0.505	1.240 [1.045, 1.471] (OR)
Constipation	logistic	0.248	0.107	0.021	0.90	0.782	1.281 [1.038, 1.581] (OR)
UPDRS4_scaled	mixed	0.040	0.017	0.022	0.27	0.821	0.040 [0.006, 0.074]
MMSE	mixed	0.120	0.056	0.033	0.59	1.000	0.120 [0.009, 0.231]
Daytime_Sleepiness	logistic	-0.294	0.140	0.036	0.26	1.000	0.745 [0.566, 0.980] (OR)
Wearing_Off	survival	0.103	0.054	0.057	0.47	1.000	1.109 [0.997, 1.233] (HR)
Wearing_Off	logistic	0.255	0.142	0.072	0.07	1.000	1.291 [0.978, 1.705] (OR)
pRBD	survival	-0.212	0.134	0.115	0.32	1.000	0.809 [0.622, 1.053] (HR)
UPDRS1_scaled	mixed	-0.032	0.020	0.117	0.60	1.000	-0.032 [-0.072, 0.008]
Depression	survival	0.065	0.074	0.386	0.11	1.000	1.067 [0.922, 1.234] (HR)
UPDRS1_scaled	linear	0.026	0.035	0.450	0.45	1.000	0.026 [-0.042, 0.094]
SEADL70	logistic	0.192	0.277	0.488	0.98	1.000	1.212 [0.704, 2.086] (OR)
SEADL	mixed	0.129	0.221	0.560	0.26	1.000	0.129 [-0.305, 0.563]
Hyposmia	logistic	0.105	0.181	0.563	0.44	1.000	1.111 [0.778, 1.585] (OR)
Hyposmia	survival	-0.125	0.223	0.575	0.76	1.000	0.882 [0.570, 1.366] (HR)
HY	mixed	0.007	0.012	0.590	0.98	1.000	0.007 [-0.017, 0.031]
SEADL	linear	-0.100	0.214	0.640	0.65	1.000	-0.100 [-0.519, 0.319]
pRBD	logistic	-0.093	0.242	0.702	0.16	1.000	0.912 [0.567, 1.465] (OR)
Insomnia	survival	0.024	0.076	0.750	0.57	1.000	1.025 [0.882, 1.190] (HR)
RLS	logistic	-0.027	0.137	0.843	0.89	1.000	0.973 [0.743, 1.274] (OR)
MMSE	linear	-0.003	0.070	0.968	0.31	1.000	-0.003 [-0.140, 0.135]
Cognitive_Impairment	logistic	-0.124	0.201	0.538	0.03		0.883 [0.596, 1.311] (OR)
SEADL70	survival	0.058	0.161	0.717	0.01		1.060 [0.773, 1.453] (HR)
HY	linear	0.000	0.026	0.992	0.01		-0.000 [-0.051, 0.051]

SE, standard error; P-adj, Bonferroni adjusted P; QEp, test of homogeneity; Mean [95%CI], Mean and 95% confidence interval of the difference in each scale. HR, hazard ratio; OR, odds ratio.
* Test of homogeneity rejected (<0.05).
UPDRS, Unified Parkinson's Disease Rating Scale; MoCA, Montreal Cognitive Assessment; MMSE, Mini-Mental State examination; RLS, restless legs syndrome; RBD, REM behavior disorder; HY Hoehn and Yahr scale; SEADL Modified Schwab and England Activities of Daily Living Scale.

Associations between sex and dyskinesia in survival models with further adjustment

Supplemental Table. Associations between sex and dyskinesia in survival models with further adjustment

Further adjusted variable	Beta	SE	P	Test of homogeneity
None (Base Model)	0.284	0.082	0.0005	0.37
BMI, kg/m2	0.249	0.073	0.0007	0.45
Weight at baseline, kg	0.156	0.083	0.0583	0.48
Levodopa dosage, mg/day	0.380	0.117	0.0012	0.15
Levodopa equivalent dose, /day	0.360	0.104	0.0006	0.21

Participants were 2281 people and 845 incidences of dyskinesia were observed during follow-up periods (PPMI, PDBP and NET_PD_LS1.)
The baseline model was adjusted for a linear and a square age; a linear and a square disease duration; a levodopa usage indicator; and a dopamine agonist usage indicator.

R model specifications

Supplemental Table. R model specifications

Study	Analysis	Outcome	Model
PPMI	Baseline analysis	Hyposmia	Y ~ FEMALE + Age + DiseaseDuration + I(DiseaseDuration^2) + I(Age^2)
PDBP	Baseline analysis	Hyposmia	Y ~ FEMALE + Age + DiseaseDuration + I(DiseaseDuration^2) + I(Age^2)
UDALL_PENN	Baseline analysis	Hyposmia	Y ~ FEMALE + Age + DiseaseDuration + LEVODOPA + AGONIST + I(DiseaseDuration^2) + I(Age^2)
PARKWEST	Baseline analysis	Cognitive_Impairment	Y ~ FEMALE + Age + DiseaseDuration + LEVODOPA + AGONIST + I(DiseaseDuration^2) + I(Age^2)
DATATOP	Baseline analysis	Cognitive_Impairment	Y ~ FEMALE + Age + DiseaseDuration + LEVODOPA + AGONIST + I(DiseaseDuration^2) + I(Age^2)
NET_PD_LS1	Baseline analysis	Cognitive_Impairment	Y ~ FEMALE + Age + DiseaseDuration + LEVODOPA + AGONIST + I(DiseaseDuration^2) + I(Age^2)
PDBP	Baseline analysis	Cognitive_Impairment	Y ~ FEMALE + Age + DiseaseDuration + I(DiseaseDuration^2) + I(Age^2)
HBS	Baseline analysis	Cognitive_Impairment	Y ~ FEMALE + Age + DiseaseDuration + LEVODOPA + AGONIST + I(DiseaseDuration^2) + I(Age^2)
PARKFIT	Baseline analysis	Cognitive_Impairment	Y ~ FEMALE + Age + DiseaseDuration + I(DiseaseDuration^2) + I(Age^2)
PROPARK	Baseline analysis	Cognitive_Impairment	Y ~ FEMALE + Age + DiseaseDuration + LEVODOPA + AGONIST + I(DiseaseDuration^2) + I(Age^2)
NET_PD_LS1	Baseline analysis	Wearing_Off	Y ~ FEMALE + Age + DiseaseDuration + LEVODOPA + AGONIST + I(DiseaseDuration^2) + I(Age^2)
DIGPD	Baseline analysis	Wearing_Off	Y ~ FEMALE + Age + DiseaseDuration + LEVODOPA + AGONIST + I(DiseaseDuration^2) + I(Age^2)
PDBP	Baseline analysis	Wearing_Off	Y ~ FEMALE + Age + DiseaseDuration + I(DiseaseDuration^2) + I(Age^2)
HBS	Baseline analysis	Wearing_Off	Y ~ FEMALE + Age + DiseaseDuration + LEVODOPA + AGONIST + I(DiseaseDuration^2) + I(Age^2)
PROPARK	Baseline analysis	Wearing_Off	Y ~ FEMALE + Age + DiseaseDuration + LEVODOPA + AGONIST + I(DiseaseDuration^2) + I(Age^2)
UDALL_PENN	Baseline analysis	Wearing_Off	Y ~ FEMALE + Age + DiseaseDuration + LEVODOPA + AGONIST + I(DiseaseDuration^2) + I(Age^2)
NET_PD_LS1	Baseline analysis	Dyskinesia	Y ~ FEMALE + Age + DiseaseDuration + LEVODOPA + AGONIST + I(DiseaseDuration^2) + I(Age^2)
PDBP	Baseline analysis	Dyskinesia	Y ~ FEMALE + Age + DiseaseDuration + I(DiseaseDuration^2) + I(Age^2)
HBS	Baseline analysis	Dyskinesia	Y ~ FEMALE + Age + DiseaseDuration + LEVODOPA + AGONIST + I(DiseaseDuration^2) + I(Age^2)
PROPARK	Baseline analysis	Dyskinesia	Y ~ FEMALE + Age + DiseaseDuration + LEVODOPA + AGONIST + I(DiseaseDuration^2) + I(Age^2)
UDALL_PENN	Baseline analysis	Dyskinesia	Y ~ FEMALE + Age + DiseaseDuration + LEVODOPA + AGONIST + I(DiseaseDuration^2) + I(Age^2)
PPMI	Baseline analysis	Depression	Y ~ FEMALE + Age + DiseaseDuration + I(DiseaseDuration^2) + I(Age^2)
PreCEPT_PostCEPT	Baseline analysis	Depression	Y ~ FEMALE + Age + DiseaseDuration + LEVODOPA + AGONIST + I(DiseaseDuration^2) + I(Age^2)
PARKWEST	Baseline analysis	Depression	Y ~ FEMALE + Age + DiseaseDuration + LEVODOPA + AGONIST + I(DiseaseDuration^2) + I(Age^2)
PICNICS	Baseline analysis	Depression	Y ~ FEMALE + Age + DiseaseDuration + LEVODOPA + AGONIST + I(DiseaseDuration^2) + I(Age^2)
NET_PD_LS1	Baseline analysis	Depression	Y ~ FEMALE + Age + DiseaseDuration + LEVODOPA + AGONIST + I(DiseaseDuration^2) + I(Age^2)
DIGPD	Baseline analysis	Depression	Y ~ FEMALE + Age + DiseaseDuration + LEVODOPA + AGONIST + I(DiseaseDuration^2) + I(Age^2)
PDBP	Baseline analysis	Depression	Y ~ FEMALE + Age + DiseaseDuration + I(DiseaseDuration^2) + I(Age^2)
HBS	Baseline analysis	Depression	Y ~ FEMALE + Age + DiseaseDuration + LEVODOPA + AGONIST + I(DiseaseDuration^2) + I(Age^2)

PROPARK	Baseline analysis	Depression	Y ~ FEMALE + Age + DiseaseDuration + LEVODOPA + AGONIST + I(DiseaseDuration^2) + I(Age^2)
UDALL_PENN	Baseline analysis	Depression	Y ~ FEMALE + Age + DiseaseDuration + LEVODOPA + AGONIST + I(DiseaseDuration^2) + I(Age^2)
PPMI	Baseline analysis	RLS	Y ~ FEMALE + Age + DiseaseDuration + I(DiseaseDuration^2) + I(Age^2)
PARKWEST	Baseline analysis	RLS	Y ~ FEMALE + Age + DiseaseDuration + LEVODOPA + AGONIST + I(DiseaseDuration^2) + I(Age^2)
DIGPD	Baseline analysis	RLS	Y ~ FEMALE + Age + DiseaseDuration + LEVODOPA + AGONIST + I(DiseaseDuration^2) + I(Age^2)
PDBP	Baseline analysis	RLS	Y ~ FEMALE + Age + DiseaseDuration + I(DiseaseDuration^2) + I(Age^2)
HBS	Baseline analysis	RLS	Y ~ FEMALE + Age + DiseaseDuration + LEVODOPA + AGONIST + I(DiseaseDuration^2) + I(Age^2)
PPMI	Baseline analysis	Constipation	Y ~ FEMALE + Age + DiseaseDuration + I(DiseaseDuration^2) + I(Age^2)
PARKWEST	Baseline analysis	Constipation	Y ~ FEMALE + Age + DiseaseDuration + LEVODOPA + AGONIST + I(DiseaseDuration^2) + I(Age^2)
PICNICS	Baseline analysis	Constipation	Y ~ FEMALE + Age + DiseaseDuration + LEVODOPA + AGONIST + I(DiseaseDuration^2) + I(Age^2)
DIGPD	Baseline analysis	Constipation	Y ~ FEMALE + Age + DiseaseDuration + LEVODOPA + AGONIST + I(DiseaseDuration^2) + I(Age^2)
PDBP	Baseline analysis	Constipation	Y ~ FEMALE + Age + DiseaseDuration + I(DiseaseDuration^2) + I(Age^2)
PROPARK	Baseline analysis	Constipation	Y ~ FEMALE + Age + DiseaseDuration + LEVODOPA + AGONIST + I(DiseaseDuration^2) + I(Age^2)
PPMI	Baseline analysis	pRBD	Y ~ FEMALE + Age + DiseaseDuration + I(DiseaseDuration^2) + I(Age^2)
PDBP	Baseline analysis	pRBD	Y ~ FEMALE + Age + DiseaseDuration + I(DiseaseDuration^2) + I(Age^2)
PPMI	Baseline analysis	Daytime_Sleepiness	Y ~ FEMALE + Age + DiseaseDuration + I(DiseaseDuration^2) + I(Age^2)
PARKWEST	Baseline analysis	Daytime_Sleepiness	Y ~ FEMALE + Age + DiseaseDuration + LEVODOPA + AGONIST + I(DiseaseDuration^2) + I(Age^2)
DIGPD	Baseline analysis	Daytime_Sleepiness	Y ~ FEMALE + Age + DiseaseDuration + LEVODOPA + AGONIST + I(DiseaseDuration^2) + I(Age^2)
PDBP	Baseline analysis	Daytime_Sleepiness	Y ~ FEMALE + Age + DiseaseDuration + I(DiseaseDuration^2) + I(Age^2)
PROPARK	Baseline analysis	Daytime_Sleepiness	Y ~ FEMALE + Age + DiseaseDuration + LEVODOPA + AGONIST + I(DiseaseDuration^2) + I(Age^2)
PPMI	Baseline analysis	Insomnia	Y ~ FEMALE + Age + DiseaseDuration + I(DiseaseDuration^2) + I(Age^2)
PARKWEST	Baseline analysis	Insomnia	Y ~ FEMALE + Age + DiseaseDuration + LEVODOPA + AGONIST + I(DiseaseDuration^2) + I(Age^2)
DATATOP	Baseline analysis	Insomnia	Y ~ FEMALE + Age + DiseaseDuration + LEVODOPA + AGONIST + I(DiseaseDuration^2) + I(Age^2)
PICNICS	Baseline analysis	Insomnia	Y ~ FEMALE + Age + DiseaseDuration + LEVODOPA + AGONIST + I(DiseaseDuration^2) + I(Age^2)
DIGPD	Baseline analysis	Insomnia	Y ~ FEMALE + Age + DiseaseDuration + LEVODOPA + AGONIST + I(DiseaseDuration^2) + I(Age^2)
PDBP	Baseline analysis	Insomnia	Y ~ FEMALE + Age + DiseaseDuration + I(DiseaseDuration^2) + I(Age^2)
HBS	Baseline analysis	Insomnia	Y ~ FEMALE + Age + DiseaseDuration + LEVODOPA + AGONIST + I(DiseaseDuration^2) + I(Age^2)
PROPARK	Baseline analysis	Insomnia	Y ~ FEMALE + Age + DiseaseDuration + LEVODOPA + AGONIST + I(DiseaseDuration^2) + I(Age^2)
PDBP	Baseline analysis	SEADL70	Y ~ FEMALE + Age + DiseaseDuration + I(DiseaseDuration^2) + I(Age^2)
UDALL_PENN	Baseline analysis	SEADL70	Y ~ FEMALE + Age + DiseaseDuration + LEVODOPA + AGONIST + I(DiseaseDuration^2) + I(Age^2)
PPMI	Baseline analysis	UPDRS_scaled	Y ~ FEMALE + Age + DiseaseDuration + I(DiseaseDuration^2) + I(Age^2)
PreCEPT_PostCEPT	Baseline analysis	UPDRS_scaled	Y ~ FEMALE + Age + DiseaseDuration + LEVODOPA + AGONIST + I(DiseaseDuration^2) + I(Age^2)
PARKWEST	Baseline analysis	UPDRS_scaled	Y ~ FEMALE + Age + DiseaseDuration + LEVODOPA + AGONIST + I(DiseaseDuration^2) + I(Age^2)
DATATOP	Baseline analysis	UPDRS_scaled	Y ~ FEMALE + Age + DiseaseDuration + LEVODOPA + AGONIST + I(DiseaseDuration^2) + I(Age^2)
PICNICS	Baseline analysis	UPDRS_scaled	Y ~ FEMALE + Age + DiseaseDuration + LEVODOPA + AGONIST + I(DiseaseDuration^2) + I(Age^2)
NET_PD_LS1	Baseline analysis	UPDRS_scaled	Y ~ FEMALE + Age + DiseaseDuration + LEVODOPA + AGONIST + I(DiseaseDuration^2) + I(Age^2)

DIGPD	Baseline analysis	UPDRS_scaled	Y ~ FEMALE + Age + DiseaseDuration + LEVODOPA + AGONIST + I(DiseaseDuration^2) + I(Age^2)
PDBP	Baseline analysis	UPDRS_scaled	Y ~ FEMALE + Age + DiseaseDuration + I(DiseaseDuration^2) + I(Age^2)
HBS	Baseline analysis	UPDRS_scaled	Y ~ FEMALE + Age + DiseaseDuration + LEVODOPA + AGONIST + I(DiseaseDuration^2) + I(Age^2)
PARKFIT	Baseline analysis	UPDRS_scaled	Y ~ FEMALE + Age + DiseaseDuration + I(DiseaseDuration^2) + I(Age^2)
UDALL_PENN	Baseline analysis	UPDRS_scaled	Y ~ FEMALE + Age + DiseaseDuration + LEVODOPA + AGONIST + I(DiseaseDuration^2) + I(Age^2)
PPMI	Baseline analysis	UPDRS1_scaled	Y ~ FEMALE + Age + DiseaseDuration + I(DiseaseDuration^2) + I(Age^2)
PreCEPT_PostCEPT	Baseline analysis	UPDRS1_scaled	Y ~ FEMALE + Age + DiseaseDuration + LEVODOPA + AGONIST + I(DiseaseDuration^2) + I(Age^2)
PARKWEST	Baseline analysis	UPDRS1_scaled	Y ~ FEMALE + Age + DiseaseDuration + LEVODOPA + AGONIST + I(DiseaseDuration^2) + I(Age^2)
NET_PD_LS1	Baseline analysis	UPDRS1_scaled	Y ~ FEMALE + Age + DiseaseDuration + LEVODOPA + AGONIST + I(DiseaseDuration^2) + I(Age^2)
DIGPD	Baseline analysis	UPDRS1_scaled	Y ~ FEMALE + Age + DiseaseDuration + LEVODOPA + AGONIST + I(DiseaseDuration^2) + I(Age^2)
PDBP	Baseline analysis	UPDRS1_scaled	Y ~ FEMALE + Age + DiseaseDuration + I(DiseaseDuration^2) + I(Age^2)
HBS	Baseline analysis	UPDRS1_scaled	Y ~ FEMALE + Age + DiseaseDuration + LEVODOPA + AGONIST + I(DiseaseDuration^2) + I(Age^2)
UDALL_PENN	Baseline analysis	UPDRS1_scaled	Y ~ FEMALE + Age + DiseaseDuration + LEVODOPA + AGONIST + I(DiseaseDuration^2) + I(Age^2)
PPMI	Baseline analysis	UPDRS2_scaled	Y ~ FEMALE + Age + DiseaseDuration + I(DiseaseDuration^2) + I(Age^2)
PreCEPT_PostCEPT	Baseline analysis	UPDRS2_scaled	Y ~ FEMALE + Age + DiseaseDuration + LEVODOPA + AGONIST + I(DiseaseDuration^2) + I(Age^2)
PARKWEST	Baseline analysis	UPDRS2_scaled	Y ~ FEMALE + Age + DiseaseDuration + LEVODOPA + AGONIST + I(DiseaseDuration^2) + I(Age^2)
NET_PD_LS1	Baseline analysis	UPDRS2_scaled	Y ~ FEMALE + Age + DiseaseDuration + LEVODOPA + AGONIST + I(DiseaseDuration^2) + I(Age^2)
DIGPD	Baseline analysis	UPDRS2_scaled	Y ~ FEMALE + Age + DiseaseDuration + LEVODOPA + AGONIST + I(DiseaseDuration^2) + I(Age^2)
PDBP	Baseline analysis	UPDRS2_scaled	Y ~ FEMALE + Age + DiseaseDuration + I(DiseaseDuration^2) + I(Age^2)
HBS	Baseline analysis	UPDRS2_scaled	Y ~ FEMALE + Age + DiseaseDuration + LEVODOPA + AGONIST + I(DiseaseDuration^2) + I(Age^2)
UDALL_PENN	Baseline analysis	UPDRS2_scaled	Y ~ FEMALE + Age + DiseaseDuration + LEVODOPA + AGONIST + I(DiseaseDuration^2) + I(Age^2)
PPMI	Baseline analysis	UPDRS3_scaled	Y ~ FEMALE + Age + DiseaseDuration + I(DiseaseDuration^2) + I(Age^2)
PreCEPT_PostCEPT	Baseline analysis	UPDRS3_scaled	Y ~ FEMALE + Age + DiseaseDuration + LEVODOPA + AGONIST + I(DiseaseDuration^2) + I(Age^2)
PARKWEST	Baseline analysis	UPDRS3_scaled	Y ~ FEMALE + Age + DiseaseDuration + LEVODOPA + AGONIST + I(DiseaseDuration^2) + I(Age^2)
NET_PD_LS1	Baseline analysis	UPDRS3_scaled	Y ~ FEMALE + Age + DiseaseDuration + LEVODOPA + AGONIST + I(DiseaseDuration^2) + I(Age^2)
DIGPD	Baseline analysis	UPDRS3_scaled	Y ~ FEMALE + Age + DiseaseDuration + LEVODOPA + AGONIST + I(DiseaseDuration^2) + I(Age^2)
PDBP	Baseline analysis	UPDRS3_scaled	Y ~ FEMALE + Age + DiseaseDuration + I(DiseaseDuration^2) + I(Age^2)
HBS	Baseline analysis	UPDRS3_scaled	Y ~ FEMALE + Age + DiseaseDuration + LEVODOPA + AGONIST + I(DiseaseDuration^2) + I(Age^2)
UDALL_PENN	Baseline analysis	UPDRS3_scaled	Y ~ FEMALE + Age + DiseaseDuration + LEVODOPA + AGONIST + I(DiseaseDuration^2) + I(Age^2)
PPMI	Baseline analysis	UPDRS4_scaled	Y ~ FEMALE + Age + DiseaseDuration + I(DiseaseDuration^2) + I(Age^2)
PARKWEST	Baseline analysis	UPDRS4_scaled	Y ~ FEMALE + Age + DiseaseDuration + LEVODOPA + AGONIST + I(DiseaseDuration^2) + I(Age^2)
NET_PD_LS1	Baseline analysis	UPDRS4_scaled	Y ~ FEMALE + Age + DiseaseDuration + LEVODOPA + AGONIST + I(DiseaseDuration^2) + I(Age^2)
DIGPD	Baseline analysis	UPDRS4_scaled	Y ~ FEMALE + Age + DiseaseDuration + LEVODOPA + AGONIST + I(DiseaseDuration^2) + I(Age^2)
PDBP	Baseline analysis	UPDRS4_scaled	Y ~ FEMALE + Age + DiseaseDuration + I(DiseaseDuration^2) + I(Age^2)
HBS	Baseline analysis	UPDRS4_scaled	Y ~ FEMALE + Age + DiseaseDuration + LEVODOPA + AGONIST + I(DiseaseDuration^2) + I(Age^2)

UDALL_PENN	Baseline analysis	UPDRS4_scaled	Y ~ FEMALE + Age + DiseaseDuration + LEVODOPA + AGONIST + I(DiseaseDuration^2) + I(Age^2)
PPMI	Baseline analysis	HY	Y ~ FEMALE + Age + DiseaseDuration + I(DiseaseDuration^2) + I(Age^2)
PreCEPT_PostCEPT	Baseline analysis	HY	Y ~ FEMALE + Age + DiseaseDuration + LEVODOPA + AGONIST + I(DiseaseDuration^2) + I(Age^2)
PARKWEST	Baseline analysis	HY	Y ~ FEMALE + Age + DiseaseDuration + LEVODOPA + AGONIST + I(DiseaseDuration^2) + I(Age^2)
DATATOP	Baseline analysis	HY	Y ~ FEMALE + Age + DiseaseDuration + LEVODOPA + AGONIST + I(DiseaseDuration^2) + I(Age^2)
PICNICS	Baseline analysis	HY	Y ~ FEMALE + Age + DiseaseDuration + LEVODOPA + AGONIST + I(DiseaseDuration^2) + I(Age^2)
NET_PD_LS1	Baseline analysis	HY	Y ~ FEMALE + Age + DiseaseDuration + LEVODOPA + AGONIST + I(DiseaseDuration^2) + I(Age^2)
DIGPD	Baseline analysis	HY	Y ~ FEMALE + Age + DiseaseDuration + LEVODOPA + AGONIST + I(DiseaseDuration^2) + I(Age^2)
PDBP	Baseline analysis	HY	Y ~ FEMALE + Age + DiseaseDuration + I(DiseaseDuration^2) + I(Age^2)
HBS	Baseline analysis	HY	Y ~ FEMALE + Age + DiseaseDuration + LEVODOPA + AGONIST + I(DiseaseDuration^2) + I(Age^2)
PARKFIT	Baseline analysis	HY	Y ~ FEMALE + Age + DiseaseDuration + I(DiseaseDuration^2) + I(Age^2)
PROPARK	Baseline analysis	HY	Y ~ FEMALE + Age + DiseaseDuration + LEVODOPA + AGONIST + I(DiseaseDuration^2) + I(Age^2)
UDALL_PENN	Baseline analysis	HY	Y ~ FEMALE + Age + DiseaseDuration + LEVODOPA + AGONIST + I(DiseaseDuration^2) + I(Age^2)
PreCEPT_PostCEPT	Baseline analysis	MMSE	Y ~ FEMALE + Age + DiseaseDuration + LEVODOPA + AGONIST + I(DiseaseDuration^2) + I(Age^2)
PARKWEST	Baseline analysis	MMSE	Y ~ FEMALE + Age + DiseaseDuration + LEVODOPA + AGONIST + I(DiseaseDuration^2) + I(Age^2)
DATATOP	Baseline analysis	MMSE	Y ~ FEMALE + Age + DiseaseDuration + LEVODOPA + AGONIST + I(DiseaseDuration^2) + I(Age^2)
PICNICS	Baseline analysis	MMSE	Y ~ FEMALE + Age + DiseaseDuration + LEVODOPA + AGONIST + I(DiseaseDuration^2) + I(Age^2)
DIGPD	Baseline analysis	MMSE	Y ~ FEMALE + Age + DiseaseDuration + LEVODOPA + AGONIST + I(DiseaseDuration^2) + I(Age^2)
HBS	Baseline analysis	MMSE	Y ~ FEMALE + Age + DiseaseDuration + LEVODOPA + AGONIST + I(DiseaseDuration^2) + I(Age^2)
PARKFIT	Baseline analysis	MMSE	Y ~ FEMALE + Age + DiseaseDuration + I(DiseaseDuration^2) + I(Age^2)
PROPARK	Baseline analysis	MMSE	Y ~ FEMALE + Age + DiseaseDuration + LEVODOPA + AGONIST + I(DiseaseDuration^2) + I(Age^2)
UDALL_PENN	Baseline analysis	MMSE	Y ~ FEMALE + Age + DiseaseDuration + LEVODOPA + AGONIST + I(DiseaseDuration^2) + I(Age^2)
PPMI	Baseline analysis	MoCA	Y ~ FEMALE + Age + DiseaseDuration + I(DiseaseDuration^2) + I(Age^2)
PDBP	Baseline analysis	MoCA	Y ~ FEMALE + Age + DiseaseDuration + I(DiseaseDuration^2) + I(Age^2)
UDALL_PENN	Baseline analysis	MoCA	Y ~ FEMALE + Age + DiseaseDuration + LEVODOPA + AGONIST + I(DiseaseDuration^2) + I(Age^2)
PPMI	Baseline analysis	SEADL	Y ~ FEMALE + Age + DiseaseDuration + I(DiseaseDuration^2) + I(Age^2)
PreCEPT_PostCEPT	Baseline analysis	SEADL	Y ~ FEMALE + Age + DiseaseDuration + LEVODOPA + AGONIST + I(DiseaseDuration^2) + I(Age^2)
PARKWEST	Baseline analysis	SEADL	Y ~ FEMALE + Age + DiseaseDuration + LEVODOPA + AGONIST + I(DiseaseDuration^2) + I(Age^2)
DATATOP	Baseline analysis	SEADL	Y ~ FEMALE + Age + DiseaseDuration + LEVODOPA + AGONIST + I(DiseaseDuration^2) + I(Age^2)
NET_PD_LS1	Baseline analysis	SEADL	Y ~ FEMALE + Age + DiseaseDuration + LEVODOPA + AGONIST + I(DiseaseDuration^2) + I(Age^2)
DIGPD	Baseline analysis	SEADL	Y ~ FEMALE + Age + DiseaseDuration + LEVODOPA + AGONIST + I(DiseaseDuration^2) + I(Age^2)
PDBP	Baseline analysis	SEADL	Y ~ FEMALE + Age + DiseaseDuration + I(DiseaseDuration^2) + I(Age^2)
UDALL_PENN	Baseline analysis	SEADL	Y ~ FEMALE + Age + DiseaseDuration + LEVODOPA + AGONIST + I(DiseaseDuration^2) + I(Age^2)
PPMI	Progression rate analysis	UPDRS_scaled	Y ~ Age + DiseaseDuration + LEVODOPA + AGONIST + FEMALE + FEMALE:DiseaseDuration + (DiseaseDuration|ID) + I(Age^2) + I(DiseaseDuration^2)

PreCEPT_PostCEPT	Progression rate analysis	UPDRS_scaled	Y ~ Age + DiseaseDuration + LEVODOPA + AGONIST + FEMALE + FEMALE:DiseaseDuration + (DiseaseDuration|ID) + I(Age^2) + I(DiseaseDuration^2)
PARKWEST	Progression rate analysis	UPDRS_scaled	Y ~ Age + DiseaseDuration + LEVODOPA + AGONIST + FEMALE + FEMALE:DiseaseDuration + (DiseaseDuration|ID) + I(Age^2) + I(DiseaseDuration^2)
DATATOP	Progression rate analysis	UPDRS_scaled	Y ~ Age + DiseaseDuration + FEMALE + FEMALE:DiseaseDuration + (DiseaseDuration|ID) + I(Age^2) + I(DiseaseDuration^2)
PICNICS	Progression rate analysis	UPDRS_scaled	Y ~ Age + DiseaseDuration + LEVODOPA + AGONIST + FEMALE + FEMALE:DiseaseDuration + (DiseaseDuration|ID) + I(Age^2) + I(DiseaseDuration^2)
NET_PD_LS1	Progression rate analysis	UPDRS_scaled	Y ~ Age + DiseaseDuration + LEVODOPA + AGONIST + FEMALE + FEMALE:DiseaseDuration + (DiseaseDuration|ID) + I(Age^2) + I(DiseaseDuration^2)
DIGPD	Progression rate analysis	UPDRS_scaled	Y ~ Age + DiseaseDuration + LEVODOPA + AGONIST + FEMALE + FEMALE:DiseaseDuration + (DiseaseDuration|ID) + I(Age^2) + I(DiseaseDuration^2)
PDBP	Progression rate analysis	UPDRS_scaled	Y ~ Age + DiseaseDuration + LEVODOPA + AGONIST + FEMALE + FEMALE:DiseaseDuration + (DiseaseDuration|ID) + I(Age^2) + I(DiseaseDuration^2)
UDALL_PENN	Progression rate analysis	UPDRS_scaled	Y ~ Age + DiseaseDuration + LEVODOPA + AGONIST + FEMALE + FEMALE:DiseaseDuration + (DiseaseDuration|ID) + I(Age^2) + I(DiseaseDuration^2)
PPMI	Progression rate analysis	UPDRS1_scaled	Y ~ Age + DiseaseDuration + LEVODOPA + AGONIST + FEMALE + FEMALE:DiseaseDuration + (DiseaseDuration|ID) + I(Age^2) + I(DiseaseDuration^2)
PreCEPT_PostCEPT	Progression rate analysis	UPDRS1_scaled	Y ~ Age + DiseaseDuration + LEVODOPA + AGONIST + FEMALE + FEMALE:DiseaseDuration + (DiseaseDuration|ID) + I(Age^2) + I(DiseaseDuration^2)
PARKWEST	Progression rate analysis	UPDRS1_scaled	Y ~ Age + DiseaseDuration + LEVODOPA + AGONIST + FEMALE + FEMALE:DiseaseDuration + (DiseaseDuration|ID) + I(Age^2) + I(DiseaseDuration^2)
NET_PD_LS1	Progression rate analysis	UPDRS1_scaled	Y ~ Age + DiseaseDuration + LEVODOPA + AGONIST + FEMALE + FEMALE:DiseaseDuration + (DiseaseDuration|ID) + I(Age^2) + I(DiseaseDuration^2)
DIGPD	Progression rate analysis	UPDRS1_scaled	Y ~ Age + DiseaseDuration + LEVODOPA + AGONIST + FEMALE + FEMALE:DiseaseDuration + (DiseaseDuration|ID) + I(Age^2) + I(DiseaseDuration^2)
PDBP	Progression rate analysis	UPDRS1_scaled	Y ~ Age + DiseaseDuration + LEVODOPA + AGONIST + FEMALE + FEMALE:DiseaseDuration + (DiseaseDuration|ID) + I(Age^2) + I(DiseaseDuration^2)
UDALL_PENN	Progression rate analysis	UPDRS1_scaled	Y ~ Age + DiseaseDuration + LEVODOPA + AGONIST + FEMALE + FEMALE:DiseaseDuration + (DiseaseDuration|ID) + I(Age^2) + I(DiseaseDuration^2)
PPMI	Progression rate analysis	UPDRS2_scaled	Y ~ Age + DiseaseDuration + LEVODOPA + AGONIST + FEMALE + FEMALE:DiseaseDuration + (DiseaseDuration|ID) + I(Age^2) + I(DiseaseDuration^2)
PreCEPT_PostCEPT	Progression rate analysis	UPDRS2_scaled	Y ~ Age + DiseaseDuration + LEVODOPA + AGONIST + FEMALE + FEMALE:DiseaseDuration + (DiseaseDuration|ID) + I(Age^2) + I(DiseaseDuration^2)
PARKWEST	Progression rate analysis	UPDRS2_scaled	Y ~ Age + DiseaseDuration + LEVODOPA + AGONIST + FEMALE + FEMALE:DiseaseDuration + (DiseaseDuration|ID) + I(Age^2) + I(DiseaseDuration^2)
NET_PD_LS1	Progression rate analysis	UPDRS2_scaled	Y ~ Age + DiseaseDuration + LEVODOPA + AGONIST + FEMALE + FEMALE:DiseaseDuration + (DiseaseDuration|ID) + I(Age^2) + I(DiseaseDuration^2)
DIGPD	Progression rate analysis	UPDRS2_scaled	Y ~ Age + DiseaseDuration + LEVODOPA + AGONIST + FEMALE + FEMALE:DiseaseDuration + (DiseaseDuration|ID) + I(Age^2) + I(DiseaseDuration^2)
PDBP	Progression rate analysis	UPDRS2_scaled	Y ~ Age + DiseaseDuration + LEVODOPA + AGONIST + FEMALE + FEMALE:DiseaseDuration + (DiseaseDuration|ID) + I(Age^2) + I(DiseaseDuration^2)
UDALL_PENN	Progression rate analysis	UPDRS2_scaled	Y ~ Age + DiseaseDuration + LEVODOPA + AGONIST + FEMALE + FEMALE:DiseaseDuration + (DiseaseDuration|ID) + I(Age^2) + I(DiseaseDuration^2)

PPMI	Progression rate analysis	UPDRS3_scaled	Y ~ Age + DiseaseDuration + LEVODOPA + AGONIST + FEMALE + FEMALE:DiseaseDuration + (DiseaseDuration|ID) + I(Age^2) + I(DiseaseDuration^2)
PreCEPT_PostCEPT	Progression rate analysis	UPDRS3_scaled	Y ~ Age + DiseaseDuration + LEVODOPA + AGONIST + FEMALE + FEMALE:DiseaseDuration + (DiseaseDuration|ID) + I(Age^2) + I(DiseaseDuration^2)
PARKWEST	Progression rate analysis	UPDRS3_scaled	Y ~ Age + DiseaseDuration + LEVODOPA + AGONIST + FEMALE + FEMALE:DiseaseDuration + (DiseaseDuration|ID) + I(Age^2) + I(DiseaseDuration^2)
NET_PD_LS1	Progression rate analysis	UPDRS3_scaled	Y ~ Age + DiseaseDuration + LEVODOPA + AGONIST + FEMALE + FEMALE:DiseaseDuration + (DiseaseDuration|ID) + I(Age^2) + I(DiseaseDuration^2)
DIGPD	Progression rate analysis	UPDRS3_scaled	Y ~ Age + DiseaseDuration + LEVODOPA + AGONIST + FEMALE + FEMALE:DiseaseDuration + (DiseaseDuration|ID) + I(Age^2) + I(DiseaseDuration^2)
PDBP	Progression rate analysis	UPDRS3_scaled	Y ~ Age + DiseaseDuration + LEVODOPA + AGONIST + FEMALE + FEMALE:DiseaseDuration + (DiseaseDuration|ID) + I(Age^2) + I(DiseaseDuration^2)
UDALL_PENN	Progression rate analysis	UPDRS3_scaled	Y ~ Age + DiseaseDuration + LEVODOPA + AGONIST + FEMALE + FEMALE:DiseaseDuration + (DiseaseDuration|ID) + I(Age^2) + I(DiseaseDuration^2)
PPMI	Progression rate analysis	UPDRS4_scaled	Y ~ Age + DiseaseDuration + LEVODOPA + AGONIST + FEMALE + FEMALE:DiseaseDuration + (DiseaseDuration|ID) + I(Age^2) + I(DiseaseDuration^2)
PARKWEST	Progression rate analysis	UPDRS4_scaled	Y ~ Age + DiseaseDuration + LEVODOPA + AGONIST + FEMALE + FEMALE:DiseaseDuration + (DiseaseDuration|ID) + I(Age^2) + I(DiseaseDuration^2)
NET_PD_LS1	Progression rate analysis	UPDRS4_scaled	Y ~ Age + DiseaseDuration + LEVODOPA + AGONIST + FEMALE + FEMALE:DiseaseDuration + (DiseaseDuration|ID) + I(Age^2) + I(DiseaseDuration^2)
DIGPD	Progression rate analysis	UPDRS4_scaled	Y ~ Age + DiseaseDuration + LEVODOPA + AGONIST + FEMALE + FEMALE:DiseaseDuration + (DiseaseDuration|ID) + I(Age^2) + I(DiseaseDuration^2)
PDBP	Progression rate analysis	UPDRS4_scaled	Y ~ Age + DiseaseDuration + LEVODOPA + AGONIST + FEMALE + FEMALE:DiseaseDuration + (DiseaseDuration|ID) + I(Age^2) + I(DiseaseDuration^2)
UDALL_PENN	Progression rate analysis	UPDRS4_scaled	Y ~ Age + DiseaseDuration + LEVODOPA + AGONIST + FEMALE + FEMALE:DiseaseDuration + (DiseaseDuration|ID) + I(Age^2) + I(DiseaseDuration^2)
PPMI	Progression rate analysis	HY	Y ~ Age + DiseaseDuration + LEVODOPA + AGONIST + FEMALE + FEMALE:DiseaseDuration + (DiseaseDuration|ID) + I(Age^2) + I(DiseaseDuration^2)
PreCEPT_PostCEPT	Progression rate analysis	HY	Y ~ Age + DiseaseDuration + LEVODOPA + AGONIST + FEMALE + FEMALE:DiseaseDuration + (DiseaseDuration|ID) + I(Age^2) + I(DiseaseDuration^2)
PARKWEST	Progression rate analysis	HY	Y ~ Age + DiseaseDuration + LEVODOPA + AGONIST + FEMALE + FEMALE:DiseaseDuration + (DiseaseDuration|ID) + I(Age^2) + I(DiseaseDuration^2)
DATATOP	Progression rate analysis	HY	Y ~ Age + DiseaseDuration + FEMALE + FEMALE:DiseaseDuration + (DiseaseDuration|ID) + I(Age^2) + I(DiseaseDuration^2)
PICNICS	Progression rate analysis	HY	Y ~ Age + DiseaseDuration + LEVODOPA + AGONIST + FEMALE + FEMALE:DiseaseDuration + (DiseaseDuration|ID) + I(Age^2) + I(DiseaseDuration^2)
NET_PD_LS1	Progression rate analysis	HY	Y ~ Age + DiseaseDuration + LEVODOPA + AGONIST + FEMALE + FEMALE:DiseaseDuration + (DiseaseDuration|ID) + I(Age^2) + I(DiseaseDuration^2)
DIGPD	Progression rate analysis	HY	Y ~ Age + DiseaseDuration + LEVODOPA + AGONIST + FEMALE + FEMALE:DiseaseDuration + (DiseaseDuration|ID) + I(Age^2) + I(DiseaseDuration^2)
PDBP	Progression rate analysis	HY	Y ~ Age + DiseaseDuration + LEVODOPA + AGONIST + FEMALE + FEMALE:DiseaseDuration + (DiseaseDuration|ID) + I(Age^2) + I(DiseaseDuration^2)
PROPARK	Progression rate analysis	HY	Y ~ Age + DiseaseDuration + LEVODOPA + AGONIST + FEMALE + FEMALE:DiseaseDuration + (DiseaseDuration|ID) + I(Age^2) + I(DiseaseDuration^2)

UDALL_PENN	Progression rate analysis	HY	Y ~ Age + DiseaseDuration + LEVODOPA + AGONIST + FEMALE + FEMALE:DiseaseDuration + (DiseaseDuration|ID) + I(Age^2) + I(DiseaseDuration^2)
PreCEPT_PostCEPT	Progression rate analysis	MMSE	Y ~ Age + DiseaseDuration + LEVODOPA + AGONIST + FEMALE + FEMALE:DiseaseDuration + (DiseaseDuration|ID) + I(Age^2) + I(DiseaseDuration^2)
PARKWEST	Progression rate analysis	MMSE	Y ~ Age + DiseaseDuration + LEVODOPA + AGONIST + FEMALE + FEMALE:DiseaseDuration + (DiseaseDuration|ID) + I(Age^2) + I(DiseaseDuration^2)
DATATOP	Progression rate analysis	MMSE	Y ~ Age + DiseaseDuration + FEMALE + FEMALE:DiseaseDuration + (DiseaseDuration|ID) + I(Age^2) + I(DiseaseDuration^2)
DIGPD	Progression rate analysis	MMSE	Y ~ Age + DiseaseDuration + LEVODOPA + AGONIST + FEMALE + FEMALE:DiseaseDuration + (DiseaseDuration|ID) + I(Age^2) + I(DiseaseDuration^2)
PROPARK	Progression rate analysis	MMSE	Y ~ Age + DiseaseDuration + LEVODOPA + AGONIST + FEMALE + FEMALE:DiseaseDuration + (DiseaseDuration|ID) + I(Age^2) + I(DiseaseDuration^2)
PPMI	Progression rate analysis	MoCA	Y ~ Age + DiseaseDuration + LEVODOPA + AGONIST + FEMALE + FEMALE:DiseaseDuration + (DiseaseDuration|ID) + I(Age^2) + I(DiseaseDuration^2)
PreCEPT_PostCEPT	Progression rate analysis	MoCA	Y ~ Age + DiseaseDuration + LEVODOPA + AGONIST + FEMALE + FEMALE:DiseaseDuration + (DiseaseDuration|ID) + I(Age^2) + I(DiseaseDuration^2)
PDBP	Progression rate analysis	MoCA	Y ~ Age + DiseaseDuration + LEVODOPA + AGONIST + FEMALE + FEMALE:DiseaseDuration + (DiseaseDuration|ID) + I(Age^2) + I(DiseaseDuration^2)
UDALL_PENN	Progression rate analysis	MoCA	Y ~ Age + DiseaseDuration + LEVODOPA + AGONIST + FEMALE + FEMALE:DiseaseDuration + (DiseaseDuration|ID) + I(Age^2) + I(DiseaseDuration^2)
PPMI	Progression rate analysis	SEADL	Y ~ Age + DiseaseDuration + LEVODOPA + AGONIST + FEMALE + FEMALE:DiseaseDuration + (DiseaseDuration|ID) + I(Age^2) + I(DiseaseDuration^2)
PreCEPT_PostCEPT	Progression rate analysis	SEADL	Y ~ Age + DiseaseDuration + LEVODOPA + AGONIST + FEMALE + FEMALE:DiseaseDuration + (DiseaseDuration|ID) + I(Age^2) + I(DiseaseDuration^2)
PARKWEST	Progression rate analysis	SEADL	Y ~ Age + DiseaseDuration + LEVODOPA + AGONIST + FEMALE + FEMALE:DiseaseDuration + (DiseaseDuration|ID) + I(Age^2) + I(DiseaseDuration^2)
DATATOP	Progression rate analysis	SEADL	Y ~ Age + DiseaseDuration + FEMALE + FEMALE:DiseaseDuration + (DiseaseDuration|ID) + I(Age^2) + I(DiseaseDuration^2)
NET_PD_LS1	Progression rate analysis	SEADL	Y ~ Age + DiseaseDuration + LEVODOPA + AGONIST + FEMALE + FEMALE:DiseaseDuration + (DiseaseDuration|ID) + I(Age^2) + I(DiseaseDuration^2)
DIGPD	Progression rate analysis	SEADL	Y ~ Age + DiseaseDuration + LEVODOPA + AGONIST + FEMALE + FEMALE:DiseaseDuration + (DiseaseDuration|ID) + I(Age^2) + I(DiseaseDuration^2)
PDBP	Progression rate analysis	SEADL	Y ~ Age + DiseaseDuration + LEVODOPA + AGONIST + FEMALE + FEMALE:DiseaseDuration + (DiseaseDuration|ID) + I(Age^2) + I(DiseaseDuration^2)
UDALL_PENN	Progression rate analysis	SEADL	Y ~ Age + DiseaseDuration + LEVODOPA + AGONIST + FEMALE + FEMALE:DiseaseDuration + (DiseaseDuration|ID) + I(Age^2) + I(DiseaseDuration^2)
PPMI	Survival analysis	Hyposmia	Surv(TSTART, TSTOP, event == 1) ~ FEMALE + Age + DiseaseDuration + LEVODOPA + I(Age^2) + I(DiseaseDuration^2)
PreCEPT_PostCEPT	Survival analysis	Hyposmia	Surv(TSTART, TSTOP, event == 1) ~ FEMALE + Age + DiseaseDuration + LEVODOPA + AGONIST + I(Age^2) + I(DiseaseDuration^2)
PDBP	Survival analysis	Hyposmia	Surv(TSTART, TSTOP, event == 1) ~ FEMALE + Age + DiseaseDuration + LEVODOPA + AGONIST + I(Age^2) + I(DiseaseDuration^2)
PPMI	Survival analysis	Cognitive_Impairment	Surv(TSTART, TSTOP, event == 1) ~ FEMALE + Age + DiseaseDuration + LEVODOPA + I(Age^2) + I(DiseaseDuration^2)
PreCEPT_PostCEPT	Survival analysis	Cognitive_Impairment	Surv(TSTART, TSTOP, event == 1) ~ FEMALE + Age + DiseaseDuration + LEVODOPA + AGONIST + I(Age^2) + I(DiseaseDuration^2)
PARKWEST	Survival analysis	Cognitive_Impairment	Surv(TSTART, TSTOP, event == 1) ~ FEMALE + Age + DiseaseDuration + LEVODOPA + AGONIST + I(Age^2) + I(DiseaseDuration^2)
DATATOP	Survival analysis	Cognitive_Impairment	Surv(TSTART, TSTOP, event == 1) ~ FEMALE + Age + DiseaseDuration + LEVODOPA + AGONIST + I(Age^2) + I(DiseaseDuration^2)

PICNICS	Survival analysis	Cognitive_Impairment	Surv(TSTART, TSTOP, event == 1) ~ FEMALE + Age + DiseaseDuration + LEVODOPA + AGONIST + I(Age^2) + I(DiseaseDuration^2)
NET_PD_LS1	Survival analysis	Cognitive_Impairment	Surv(TSTART, TSTOP, event == 1) ~ FEMALE + Age + DiseaseDuration + LEVODOPA + AGONIST + I(Age^2) + I(DiseaseDuration^2)
PDBP	Survival analysis	Cognitive_Impairment	Surv(TSTART, TSTOP, event == 1) ~ FEMALE + Age + DiseaseDuration + LEVODOPA + AGONIST + I(Age^2) + I(DiseaseDuration^2)
HBS	Survival analysis	Cognitive_Impairment	Surv(TSTART, TSTOP, event == 1) ~ FEMALE + Age + DiseaseDuration + LEVODOPA + AGONIST + I(Age^2) + I(DiseaseDuration^2)
PROPARK	Survival analysis	Cognitive_Impairment	Surv(TSTART, TSTOP, event == 1) ~ FEMALE + Age + DiseaseDuration + LEVODOPA + AGONIST + I(Age^2) + I(DiseaseDuration^2)
UDALL_PENN	Survival analysis	Cognitive_Impairment	Surv(TSTART, TSTOP, event == 1) ~ FEMALE + Age + DiseaseDuration + LEVODOPA + AGONIST + I(Age^2) + I(DiseaseDuration^2)
PPMI	Survival analysis	Wearing_Off	Surv(TSTART, TSTOP, event == 1) ~ FEMALE + Age + DiseaseDuration + I(Age^2) + I(DiseaseDuration^2)
PreCEPT_PostCEPT	Survival analysis	Wearing_Off	Surv(TSTART, TSTOP, event == 1) ~ FEMALE + Age + DiseaseDuration + LEVODOPA + AGONIST + I(Age^2) + I(DiseaseDuration^2)
PARKWEST	Survival analysis	Wearing_Off	Surv(TSTART, TSTOP, event == 1) ~ FEMALE + Age + DiseaseDuration + LEVODOPA + AGONIST + I(Age^2) + I(DiseaseDuration^2)
PICNICS	Survival analysis	Wearing_Off	Surv(TSTART, TSTOP, event == 1) ~ FEMALE + Age + DiseaseDuration + LEVODOPA + AGONIST + I(Age^2) + I(DiseaseDuration^2)
NET_PD_LS1	Survival analysis	Wearing_Off	Surv(TSTART, TSTOP, event == 1) ~ FEMALE + Age + DiseaseDuration + LEVODOPA + AGONIST + I(Age^2) + I(DiseaseDuration^2)
DIGPD	Survival analysis	Wearing_Off	Surv(TSTART, TSTOP, event == 1) ~ FEMALE + Age + DiseaseDuration + LEVODOPA + AGONIST + I(Age^2) + I(DiseaseDuration^2)
PDBP	Survival analysis	Wearing_Off	Surv(TSTART, TSTOP, event == 1) ~ FEMALE + Age + DiseaseDuration + LEVODOPA + AGONIST + I(Age^2) + I(DiseaseDuration^2)
HBS	Survival analysis	Wearing_Off	Surv(TSTART, TSTOP, event == 1) ~ FEMALE + Age + DiseaseDuration + LEVODOPA + AGONIST + I(Age^2) + I(DiseaseDuration^2)
PROPARK	Survival analysis	Wearing_Off	Surv(TSTART, TSTOP, event == 1) ~ FEMALE + Age + DiseaseDuration + LEVODOPA + AGONIST + I(Age^2) + I(DiseaseDuration^2)
UDALL_PENN	Survival analysis	Wearing_Off	Surv(TSTART, TSTOP, event == 1) ~ FEMALE + Age + DiseaseDuration + LEVODOPA + AGONIST + I(Age^2) + I(DiseaseDuration^2)
PPMI	Survival analysis	Dyskinesia	Surv(TSTART, TSTOP, event == 1) ~ FEMALE + Age + DiseaseDuration + LEVODOPA + I(Age^2) + I(DiseaseDuration^2)
PreCEPT_PostCEPT	Survival analysis	Dyskinesia	Surv(TSTART, TSTOP, event == 1) ~ FEMALE + Age + DiseaseDuration + LEVODOPA + AGONIST + I(Age^2) + I(DiseaseDuration^2)
PARKWEST	Survival analysis	Dyskinesia	Surv(TSTART, TSTOP, event == 1) ~ FEMALE + Age + DiseaseDuration + LEVODOPA + AGONIST + I(Age^2) + I(DiseaseDuration^2)
NET_PD_LS1	Survival analysis	Dyskinesia	Surv(TSTART, TSTOP, event == 1) ~ FEMALE + Age + DiseaseDuration + LEVODOPA + AGONIST + I(Age^2) + I(DiseaseDuration^2)
DIGPD	Survival analysis	Dyskinesia	Surv(TSTART, TSTOP, event == 1) ~ FEMALE + Age + DiseaseDuration + LEVODOPA + AGONIST + I(Age^2) + I(DiseaseDuration^2)
PDBP	Survival analysis	Dyskinesia	Surv(TSTART, TSTOP, event == 1) ~ FEMALE + Age + DiseaseDuration + LEVODOPA + AGONIST + I(Age^2) + I(DiseaseDuration^2)
HBS	Survival analysis	Dyskinesia	Surv(TSTART, TSTOP, event == 1) ~ FEMALE + Age + DiseaseDuration + LEVODOPA + AGONIST + I(Age^2) + I(DiseaseDuration^2)
PROPARK	Survival analysis	Dyskinesia	Surv(TSTART, TSTOP, event == 1) ~ FEMALE + Age + DiseaseDuration + LEVODOPA + AGONIST + I(Age^2) + I(DiseaseDuration^2)
UDALL_PENN	Survival analysis	Dyskinesia	Surv(TSTART, TSTOP, event == 1) ~ FEMALE + Age + DiseaseDuration + LEVODOPA + AGONIST + I(Age^2) + I(DiseaseDuration^2)
PPMI	Survival analysis	Depression	Surv(TSTART, TSTOP, event == 1) ~ FEMALE + Age + DiseaseDuration + I(Age^2) + I(DiseaseDuration^2)
PreCEPT_PostCEPT	Survival analysis	Depression	Surv(TSTART, TSTOP, event == 1) ~ FEMALE + Age + DiseaseDuration + LEVODOPA + AGONIST + I(Age^2) + I(DiseaseDuration^2)
PARKWEST	Survival analysis	Depression	Surv(TSTART, TSTOP, event == 1) ~ FEMALE + Age + DiseaseDuration + LEVODOPA + AGONIST + I(Age^2) + I(DiseaseDuration^2)
DATATOP	Survival analysis	Depression	Surv(TSTART, TSTOP, event == 1) ~ FEMALE + Age + DiseaseDuration + LEVODOPA + AGONIST + I(Age^2) + I(DiseaseDuration^2)
PICNICS	Survival analysis	Depression	Surv(TSTART, TSTOP, event == 1) ~ FEMALE + Age + DiseaseDuration + LEVODOPA + AGONIST + I(Age^2) + I(DiseaseDuration^2)
NET_PD_LS1	Survival analysis	Depression	Surv(TSTART, TSTOP, event == 1) ~ FEMALE + Age + DiseaseDuration + LEVODOPA + AGONIST + I(Age^2) + I(DiseaseDuration^2)
DIGPD	Survival analysis	Depression	Surv(TSTART, TSTOP, event == 1) ~ FEMALE + Age + DiseaseDuration + LEVODOPA + AGONIST + I(Age^2) + I(DiseaseDuration^2)
PDBP	Survival analysis	Depression	Surv(TSTART, TSTOP, event == 1) ~ FEMALE + Age + DiseaseDuration + LEVODOPA + AGONIST + I(Age^2) + I(DiseaseDuration^2)

	HBS	Survival analysis	Depression	Surv(TSTART, TSTOP, event == 1) ~ FEMALE + Age + DiseaseDuration + LEVODOPA + AGONIST + I(Age^2) + I(DiseaseDuration^2)
	PROPARK	Survival analysis	Depression	Surv(TSTART, TSTOP, event == 1) ~ FEMALE + Age + DiseaseDuration + LEVODOPA + AGONIST + I(Age^2) + I(DiseaseDuration^2)
	UDALL_PENN	Survival analysis	Depression	Surv(TSTART, TSTOP, event == 1) ~ FEMALE + Age + DiseaseDuration + LEVODOPA + AGONIST + I(Age^2) + I(DiseaseDuration^2)
	PPMI	Survival analysis	RLS	Surv(TSTART, TSTOP, event == 1) ~ FEMALE + Age + DiseaseDuration + LEVODOPA + I(Age^2) + I(DiseaseDuration^2)
	PARKWEST	Survival analysis	RLS	Surv(TSTART, TSTOP, event == 1) ~ FEMALE + Age + DiseaseDuration + LEVODOPA + AGONIST + I(Age^2) + I(DiseaseDuration^2)
	DIGPD	Survival analysis	RLS	Surv(TSTART, TSTOP, event == 1) ~ FEMALE + Age + DiseaseDuration + LEVODOPA + AGONIST + I(Age^2) + I(DiseaseDuration^2)
	PDBP	Survival analysis	RLS	Surv(TSTART, TSTOP, event == 1) ~ FEMALE + Age + DiseaseDuration + LEVODOPA + AGONIST + I(Age^2) + I(DiseaseDuration^2)
	HBS	Survival analysis	RLS	Surv(TSTART, TSTOP, event == 1) ~ FEMALE + Age + DiseaseDuration + LEVODOPA + AGONIST + I(Age^2) + I(DiseaseDuration^2)
	PPMI	Survival analysis	Constipation	Surv(TSTART, TSTOP, event == 1) ~ FEMALE + Age + DiseaseDuration + I(Age^2) + I(DiseaseDuration^2)
	PreCEPT_PostCEPT	Survival analysis	Constipation	Surv(TSTART, TSTOP, event == 1) ~ FEMALE + Age + DiseaseDuration + LEVODOPA + AGONIST + I(Age^2) + I(DiseaseDuration^2)
	PARKWEST	Survival analysis	Constipation	Surv(TSTART, TSTOP, event == 1) ~ FEMALE + Age + DiseaseDuration + LEVODOPA + AGONIST + I(Age^2) + I(DiseaseDuration^2)
	PICNICS	Survival analysis	Constipation	Surv(TSTART, TSTOP, event == 1) ~ FEMALE + Age + DiseaseDuration + LEVODOPA + AGONIST + I(Age^2) + I(DiseaseDuration^2)
	DIGPD	Survival analysis	Constipation	Surv(TSTART, TSTOP, event == 1) ~ FEMALE + Age + DiseaseDuration + LEVODOPA + AGONIST + I(Age^2) + I(DiseaseDuration^2)
	PDBP	Survival analysis	Constipation	Surv(TSTART, TSTOP, event == 1) ~ FEMALE + Age + DiseaseDuration + LEVODOPA + AGONIST + I(Age^2) + I(DiseaseDuration^2)
	PROPARK	Survival analysis	Constipation	Surv(TSTART, TSTOP, event == 1) ~ FEMALE + Age + DiseaseDuration + LEVODOPA + AGONIST + I(Age^2) + I(DiseaseDuration^2)
	PPMI	Survival analysis	pRBD	Surv(TSTART, TSTOP, event == 1) ~ FEMALE + Age + DiseaseDuration + I(Age^2) + I(DiseaseDuration^2)
	PARKWEST	Survival analysis	pRBD	Surv(TSTART, TSTOP, event == 1) ~ FEMALE + Age + DiseaseDuration + LEVODOPA + AGONIST + I(Age^2) + I(DiseaseDuration^2)
	PDBP	Survival analysis	pRBD	Surv(TSTART, TSTOP, event == 1) ~ FEMALE + Age + DiseaseDuration + LEVODOPA + AGONIST + I(Age^2) + I(DiseaseDuration^2)
	PPMI	Survival analysis	Daytime_Sleepiness	Surv(TSTART, TSTOP, event == 1) ~ FEMALE + Age + DiseaseDuration + I(Age^2) + I(DiseaseDuration^2)
	PreCEPT_PostCEPT	Survival analysis	Daytime_Sleepiness	Surv(TSTART, TSTOP, event == 1) ~ FEMALE + Age + DiseaseDuration + LEVODOPA + AGONIST + I(Age^2) + I(DiseaseDuration^2)
	PARKWEST	Survival analysis	Daytime_Sleepiness	Surv(TSTART, TSTOP, event == 1) ~ FEMALE + Age + DiseaseDuration + LEVODOPA + AGONIST + I(Age^2) + I(DiseaseDuration^2)
	PICNICS	Survival analysis	Daytime_Sleepiness	Surv(TSTART, TSTOP, event == 1) ~ FEMALE + Age + DiseaseDuration + LEVODOPA + AGONIST + I(Age^2) + I(DiseaseDuration^2)
	DIGPD	Survival analysis	Daytime_Sleepiness	Surv(TSTART, TSTOP, event == 1) ~ FEMALE + Age + DiseaseDuration + LEVODOPA + AGONIST + I(Age^2) + I(DiseaseDuration^2)
	PDBP	Survival analysis	Daytime_Sleepiness	Surv(TSTART, TSTOP, event == 1) ~ FEMALE + Age + DiseaseDuration + LEVODOPA + AGONIST + I(Age^2) + I(DiseaseDuration^2)
	PROPARK	Survival analysis	Daytime_Sleepiness	Surv(TSTART, TSTOP, event == 1) ~ FEMALE + Age + DiseaseDuration + LEVODOPA + AGONIST + I(Age^2) + I(DiseaseDuration^2)
	PPMI	Survival analysis	Insomnia	Surv(TSTART, TSTOP, event == 1) ~ FEMALE + Age + DiseaseDuration + LEVODOPA + I(Age^2) + I(DiseaseDuration^2)
	PreCEPT_PostCEPT	Survival analysis	Insomnia	Surv(TSTART, TSTOP, event == 1) ~ FEMALE + Age + DiseaseDuration + LEVODOPA + AGONIST + I(Age^2) + I(DiseaseDuration^2)
	PARKWEST	Survival analysis	Insomnia	Surv(TSTART, TSTOP, event == 1) ~ FEMALE + Age + DiseaseDuration + LEVODOPA + AGONIST + I(Age^2) + I(DiseaseDuration^2)
	DATATOP	Survival analysis	Insomnia	Surv(TSTART, TSTOP, event == 1) ~ FEMALE + Age + DiseaseDuration + LEVODOPA + AGONIST + I(Age^2) + I(DiseaseDuration^2)
	PICNICS	Survival analysis	Insomnia	Surv(TSTART, TSTOP, event == 1) ~ FEMALE + Age + DiseaseDuration + LEVODOPA + AGONIST + I(Age^2) + I(DiseaseDuration^2)
	DIGPD	Survival analysis	Insomnia	Surv(TSTART, TSTOP, event == 1) ~ FEMALE + Age + DiseaseDuration + LEVODOPA + AGONIST + I(Age^2) + I(DiseaseDuration^2)
	PDBP	Survival analysis	Insomnia	Surv(TSTART, TSTOP, event == 1) ~ FEMALE + Age + DiseaseDuration + LEVODOPA + AGONIST + I(Age^2) + I(DiseaseDuration^2)
	HBS	Survival analysis	Insomnia	Surv(TSTART, TSTOP, event == 1) ~ FEMALE + Age + DiseaseDuration + LEVODOPA + AGONIST + I(Age^2) + I(DiseaseDuration^2)

PROPARK	Survival analysis	Insomnia	Surv(TSTART, TSTOP, event == 1) ~ FEMALE + Age + DiseaseDuration + LEVODOPA + AGONIST + I(Age^2) + I(DiseaseDuration^2)
PPMI	Survival analysis	SEADL70	Surv(TSTART, TSTOP, event == 1) ~ FEMALE + Age + DiseaseDuration + LEVODOPA + I(Age^2) + I(DiseaseDuration^2)
PreCEPT_PostCEPT	Survival analysis	SEADL70	Surv(TSTART, TSTOP, event == 1) ~ FEMALE + Age + DiseaseDuration + LEVODOPA + AGONIST + I(Age^2) + I(DiseaseDuration^2)
PARKWEST	Survival analysis	SEADL70	Surv(TSTART, TSTOP, event == 1) ~ FEMALE + Age + DiseaseDuration + LEVODOPA + AGONIST + I(Age^2) + I(DiseaseDuration^2)
DATATOP	Survival analysis	SEADL70	Surv(TSTART, TSTOP, event == 1) ~ FEMALE + Age + DiseaseDuration + LEVODOPA + AGONIST + I(Age^2) + I(DiseaseDuration^2)
NET_PD_LS1	Survival analysis	SEADL70	Surv(TSTART, TSTOP, event == 1) ~ FEMALE + Age + DiseaseDuration + LEVODOPA + AGONIST + I(Age^2) + I(DiseaseDuration^2)
DIGPD	Survival analysis	SEADL70	Surv(TSTART, TSTOP, event == 1) ~ FEMALE + Age + DiseaseDuration + LEVODOPA + AGONIST + I(Age^2) + I(DiseaseDuration^2)
PDBP	Survival analysis	SEADL70	Surv(TSTART, TSTOP, event == 1) ~ FEMALE + Age + DiseaseDuration + LEVODOPA + AGONIST + I(Age^2) + I(DiseaseDuration^2)
UDALL_PENN	Survival analysis	SEADL70	Surv(TSTART, TSTOP, event == 1) ~ FEMALE + Age + DiseaseDuration + LEVODOPA + AGONIST + I(Age^2) + I(DiseaseDuration^2)

UPDRS, unified parkinson's disease rating scale; MOCA, Montreal Cognitive Assessment; MMSE, Mini-Mental State examination; RLS, restless legs syndrome; RBD, REM behavior disorder; HY Hoehn and Yahr scale; SEADL Modified Schwab and England Activities of Daily Living Scale; TSTART, TSTOP, survival observation (start and stop).

Supplemental documents about the longitudinal cohorts

Descriptions

Deprenyl and Tocopherol Antioxidative Therapy of Parkinsonism (DATATOP**)** was a randomized clinical trial conducted between September 1987 and November 1989 at 28 sites across US and Canada. The primary objective was to test the efficacy of deprenyl and/or tocopherol. 800 patients with Parkinson's disease diagnosed within 5 years and not requiring symptomatic treatment were observed for up to 2 years.[1] The study was supported by a Public Health Service grant (NS24778) from the National Institute of Neurological Disorders and Stroke; by grants from the General Clinical Research Centers Program of the National Institutes of Health at Columbia University (RR00645), the University of Virginia (RR00847), the University of Pennsylvania (RR00040), the University of Iowa (RR00059), Ohio State University (RR00034), Massachusetts General Hospital (RR01066), the University of Rochester (RR00044), Brown University (RR02038), Oregon Health Sciences University (RR00334), Baylor College of Medicine (RR00350), the University of California, San Diego (RR00827), Johns Hopkins University (RR00035), the University of Michigan (RR00042), and Washington University (RR00036); the Parkinson's Disease Foundation at Columbia-Presbyterian Medical Center, New York; the National Parkinson Foundation, Miami; the Parkinson Foundation of Canada, Toronto; the United Parkinson Foundation, Chicago; the American Parkinson's Disease Association, New York; and the University of Rochester, Rochester, N.Y.

Drug Interaction with Genes in Parkinson's Disease (DIGPD**)** is a cohort with 413 patients with Parkinson's disease diagnosed by UK Parkinson's disease society brain bank clinical diagnostic (UKPDSBB) criteria with disease duration less than 5 years at the entry.[2] It is an ongoing study since 2009, and the participants are followed for up to 7 years at eight sites in France. (Corvol et al., in press in Neurology). DNA samples were collected from all of them. DIGPD is sponsored by Assistance Publique Hôpitaux de Paris, funded by a grant from the French Ministry of Health (PHRC 2008, AOM08010) and a grant from the Agence Nationale pour la Sécurité des Médicaments (ANSM 2013).

Harvard Biomarkers Study (HBS) is a longitudinal case-control study. More than 2,700 individuals with early-stage PD, patients with memory impairment, and controls without neurological disease were enrolled and longitudinally phenotyped since 2008.[3] HBS was supported by the Harvard NeuroDiscovery Center, MJFF, NINDS U01NS082157, U01NS100603, and the Massachusetts Alzheimer's Disease Research Center NIA P50AG005134.

NIH Exploratory Trials in Parkinson's Disease Large Simple Study 1 (NET-PD LS1**)** was a randomized study conducted between March 2007 and September 2013 to determine if the nutritional supplement creatine slows the clinical progression of Parkinson's disease over time. 1741 patients from 50 sites in the US and Canada participated.[4] They were within 5 years from diagnosis. The plan was for them to be followed for at least 5 years, but the study ended early for futility based on an interim analysis at which point the median follow-up time was 4 years. Financial support for the LS-1 study was provided by National Institute of Neurological Disorders and Stroke (NINDS) grant U01NS43128.

Oslo PD study[Citation error] (Oslo**)** is an ongoing study since 2007, with 317 patients diagnosed with ULPDSBB criteria with modification of allowing family history. The participants are being followed up to 6 years in prospective (30 years in retrospective) at Oslo University Hospital in Norway.[5] Oslo PD is supported by the Research Council of Norway and South-Eastern Norway Regional Health Authority.

ParkFit cohort was originally a randomized trial evaluating a multifaceted behavioural change programme to increase physical activities in patients with Parkinson's disease.[6] The study conducted from September 2008 to February 2012 at a single center in the Netherlands, with 586 patients with Parkinson's disease diagnosed by UKPDSBB, with Hoehn Yahr stage 3 or lower, and with sedentary lifestyle at the entry. They were followed up for 2 years. The primary objective was concluded as not significant[6]. ParkFit is supported by ZonMw (the Netherlands Organization for Health Research and Development (75020012)) and the Michael J Fox Foundation for Parkinson's research, VGZ (health insurance company), GlaxoSmithKline, and the National Parkinson Foundation.

The Norwegian ParkWest study (ParkWest) is an ongoing prospective longitudinal multicenter cohort study of patients with incident Parkinson's disease from Western and Southern Norway, designed to study the incidence, neurobiology and prognosis of PD.[7] Between November 1st 2004 and 31st of August 2006, all new cases of Parkinson Disease within the study area (Sogn and Fjordane, Hordaland, Rogaland and Aust-Agder) were recruited, and since the start of the study 212 of these patients and their age-/sex-matched control group were followed. The Norwegian ParkWest study is supported by the Research Council of Norway, the Western Norway Regional Health Authority, Stavanger University Hospital Research Funds, and the Norwegian Parkinson's Disease Association.

The National Institute of Neurological Disorders and Stroke (NINDS) Parkinson's Disease Biomarker Program (PDBP) is aiming to discover new diagnostic and progression biomarkers for Parkinson's disease.[8] It is a combined cohort of 9

PDBP-funded research studies. The members have various stages of Parkinson's disease and recruited throughout the United States.

Parkinsonism: Incidence and Cognitive and Non-motor heterogeneity In Cambridgeshire (PICNICS) is a population-based longitudinal study of 282 incident PD cases recruited between 2008 and 2013 with ongoing follow-up at 18 month intervals.[9,10] PD cases were diagnosed based on the UKPDSBB criteria, and followed up at a single center in the UK. PICNICS has received funding from the Cure Parkinson's Trust, the Van Geest Foundation and is supported by the National Institute of Health Research Cambridge Biomedical Research Centre.

Parkinson's progression markers initiative (PPMI) is an ongoing study started on July 2010, enrolling 424 patients with Parkinson's disease diagnosed within 2 years from the study entry date.[11] The study sites are located in 33 sites across the US, Europe, Israel and Australia[11]. PPMI is supported by the Michael J Fox Foundation for Parkinson's Research.

Parkinson Research Examination of CEP1348 Trial (PreCEPT) is a clinical trial of the mixed lineage kinase inhibitor CEP-1357,4 sponsored by Cephalon, Inc. (West Chester, PA) and H. Lundbeck A/S (Valby-Copenhagen, Denmark). The study was conducted at 65 sites in North America. The trial enrolled 806 early, untreated PD patients within one year from the onset. The original trial was started in April 2002 and terminated in August 2005 due to the futility, but the participants were continuously followed-up in the prospective observational study (PostCEPT).[12]

The studies were funded by NINDS 5U01NS050095-05, Department of Defense Neurotoxin Exposure Treatment Parkinson's Research Program. Grant Number: W23RRYX7022N606, the Michael J Fox Foundation for Parkinson's research, Parkinson's Disease Foundation, Lundbeck Pharmaceuticals. Cephalon Inc, Lundbeck Inc, John Blume Foundation, Smart Family Foundation, RJG Foundation, Kinetics Foundation, National Parkinson Foundation, Amarin Neuroscience LTD, CHDI Foundation Inc, National Institutes of Health (NHGRI, NINDS), Columbia Parkinson's Disease Research Center.

Profiling Parkinson's disease study (ProPark) is an ongoing study started from May 2003. Initially, 420 patients recruited in several sites in the Netherlands by March 2006.[13] Patients were diagnosed with UKPDSBB criteria and in various disease durations at the enrollment. They are evaluated annually with the SCOPA scale. This study is funded by the Alkemade-Keuls Foundation, Stichting Parkinson Fonds, Parkinson Vereniging, The Netherlands Organisation for Health Research and Development.

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