Sex-specific progression of Parkinson's disease: A longitudinal mixed-models analysis.

Anne-Marie Hanff[1,2,3,4*](RN, MSN), Christopher McCrum[4,5](PhD), Armin Rauschenberger[6](PhD), Gloria A. Aguayo[7](MD), Claire Pauly[1,8,9](NP, MSc), Sonja R. Jónsdóttir[1,8,9](NP, MSc), Olena Tsurkalenko[1,8,9,10](MD), Maurice P. Zeegers[3,11](PhD), Anja K. Leist[12](PhD), Rejko Krüger[1,8,9](MD) on behalf of the NCER-PD consortium

1 Transversal Translational Medicine, Luxembourg Institute of Health, Strassen, Luxembourg,

2 Faculty of Science, Technology and Medicine, University of Luxembourg, Esch-sur-Alzette, Luxembourg,

3 Department of Epidemiology, CAPHRI Care and Public Health Research Institute, Maastricht University Medical Centre+, Maastricht, The Netherlands,

4 Department of Nutrition and Movement Sciences, NUTRIM School of Nutrition and Translational Research in Metabolism, Maastricht University Medical Centre+, Maastricht, The Netherlands,

5 Department of Rehabilitation Sciences, Neurorehabilitation Research Group, KU Leuven, Leuven, Belgium,

6 Biomedical Data Science, Luxembourg Centre for Systems Biomedicine, University of Luxembourg, Esch-sur-Alzette, Luxembourg,

7 Department of Precision Health, Luxembourg Institute of Health, Strassen, Luxembourg,

8 Parkinson Research Clinic, Centre Hospitalier de Luxembourg, Luxembourg, Luxembourg,

9 Translational Neurosciences, Luxembourg Centre for Systems Biomedicine, University of Luxembourg, Esch-sur-Alzette, Luxembourg,

10 Digital Medicine group, Luxembourg Institute of Health, Strassen, Luxembourg,

11 Department of Epidemiology, NUTRIM School of Nutrition and Translational Research in Metabolism, Care and Public Health Research Institute, Maastricht

12 Department of Social Sciences, University of Luxembourg, Esch-sur-Alzette, Luxembourg.

***Correspondence:**

Anne-Marie Hanff

anne-marie.hanff@lih.lu

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Abstract

BACKGROUND: Despite its relevance, the clinical progression of motor- and non-motor symptoms associated with Parkinson’s disease (PD) is poorly described and understood, particularly in relation to sex-specific differences in clinical progression.

OBJECTIVES: Identification of differential aspects in disease progression in men and women with PD.

METHODS: Linear mixed-model analyses of a total of 802 people with typical PD from the Luxembourg Parkinson’s study’s prospective cohort, stratified by sex. Marginal effects of disease duration on the outcomes (disease duration averaged over random effects) in analyses stratified by sex were estimated and illustrated for the following outcomes: MDS-UPDRS I-IV, apathy, depression, global cognition, olfaction, bodily discomfort, rapid eye movement sleep behaviour disorder, quality of sleep, dysphagia, patient-reported functional mobility, postural instability and gait disturbances and tremor. Men and women had similar age and median time of follow-up was 3 years.

RESULTS: Compared to men, we observed slower disease progression in women for cognition, apathy, quality of sleep and MDS-UPDRS II and significantly worse scores for depression and pain at baseline. Only bodily discomfort and depression (in the first ten years since diagnosis) progressed faster in women. Intensity of tremor decreased over time for both groups.

CONCLUSION: Differential progression of symptoms in men and women with PD exists and needs to be explored further. To enhance well-being in PD, we recommend considering a sex-specific approach to managing PD symptoms.

1. Background

In the 2016 Global Burden of Disease Study, the age-standardized prevalence of Parkinson's disease (PD) was 1.4 times higher in men than in women [1]. Consequently, sex-specific factors in PD merit further study. However, most research has focused on biological differences between men and women, neglecting to place these in the psychosocial context that impacts clinical care and quality of life of men and women with PD [2-4]. Therefore, the effect of sex and/or gender should be considered in designing future studies in PD [5].

While single studies [2-4] have mainly reported cross-sectional sex differences of selected symptoms in men and women with PD, a comprehensive empirical description and illustration of the motor- and non-motor symptoms associated with Parkinson's disease progression [6] has not been reported in the literature. Aiming to provide an overview of symptom and general disease progression of PD in men and women that can be easily interpreted by health professionals, we describe the progression of motor- and non-motor symptoms in men and women with typical PD participating in a large monocentric longitudinal cohort.

2. Methods

2.1 Study design, setting, participants and study size

This retrospective analysis is part of the Luxembourg Parkinson's study, a nationwide, monocentric, observational, longitudinal-prospective and dynamic cohort

[6]. The completed STROBE reporting guideline checklist [7] is included in Supplement 4.

Among the participants were people diagnosed with typical PD or Parkinson's disease dementia (PDD) according to the United Kingdom Parkinson's Disease Society Brain Bank Clinical Diagnostic Criteria [8], living in Luxembourg and the Greater Region (geographically close areas of the surrounding countries, namely Belgium, France, and Germany). Recruitment of people with typical PD started in 2015 with annual follow-ups. The Luxembourg Parkinson's Study aims at stratification and differential diagnosis of Parkinson's disease [6].

2.2 Variables, data sources and measurement

The outcomes of interest were progression (i.e., change per additional year of disease duration) of motor and non-motor symptoms. Primary outcomes included MDS-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) I-IV, apathy, depression, global cognition, nutritional status, olfaction, pain, REM sleep behaviour disorder (RBD), quality of sleep, dysphagia, patient-reported functional mobility, postural instability and gait disturbances as well as tremor. Secondary outcomes were Levodopa Equivalent Daily Dose (LEDD), health-related quality of life, weight and height. All outcomes were numerical and assessed during annual follow-ups varying by a maximum of three months to minimize seasonal influences. The progression could be distinguished from cohort or period effects as people with PD were included at different time points [9] due to the dynamic cohort study design. People with PD with complete data for time since diagnosis were included in the longitudinal analysis. Tab. 1 describes the characteristics of the outcomes and provides sources of data and details of the assessment methods.

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Table 1: Instrument, assessment types and variable name of the included constructs

Construct intended to measure	Instrument	Assessment type	Variable name
Patient-reported outcomes			
Apathy	SAS [10]	Patient-Reported Outcome Measure	spark_score
Depression	BDI-I [11]	Patient-Reported Outcome Measure	bdi_score
Dysphagia	MDT-PD [12, 13]	Clinician- Assessed Outcome Measure	mdt_score
Functional mobility	FMCS [14]	Patient-Reported Outcome Measure	FMCS_PDQ39
Health-related quality of life	PDQ-39 [15]	Patient-Reported Outcome Measure	pdq39_score
Medication	LEDD	Patient-Reported Outcome Measure	meds_da_ledd meds_da_ledd_kg
Non-motor symptoms	MDS-UPDRS I [16]	Patient-Reported and Clinician Assessed Outcome Measure	UPDRS_1
Motor symptoms	MDS-UPDRS II [16]	Patient-Reported Outcome Measure	UPDRS_2
Pain	PDQ-39 subscale bodily discomfort [15]	Patient-Reported Outcome Measure	pdq39_q36_q39_score
Quality of sleep	PDSS [17]	Patient-Reported Outcome Measure	pdss_score
Rem-sleep behavior disorder	RBDSQ [18]	Patient-Reported Outcome Measure	rem_score
Clinician assessed outcomes or performance tests			
Cognition	MoCA Total Score [19]	Performance test	MoCA_score
Motor symptoms	MDS-UPDRS III [16]	Clinician-Assessed Outcome Measure	UPDRS_3
Motor fluctuations	MDS-UPDRS IV [16]	Clinician-Assessed Outcome Measure	UPDRS_4
Weight	Weight (kg) [20]	Clinician- Assessed Outcome Measure	status_weight
Olfaction	ODOFIN Sniffin' Sticks Identification Test 16	Performance test	sniff_score
Postural instability and gait disorder	PIGD score [21, 22],	Patient-Reported and Clinician Assessed Outcome Measure	PIGD_score
Height	Height (cm) [20]	Clinician- Assessed Outcome Measure	status_height
Tremor	Tremor scale [22, 23]	Patient-Reported and Clinician Assessed Outcome Measure	trem_trem_score
Exposure			
Time variant with baseline assessment and yearly follow-up	Disease duration (y.): Date of assessment – Date of diagnosis	Interview	disease_duration
Confounder			
Time variant with baseline assessment and yearly follow-up	Time to diagnosis (y.): Date of diagnosis – Date of first motor symptoms	Interview	diagnosis_duration

Abbreviations: BDI-I: Beck Depression Inventory I, FMCS: Functional Mobility Composite Score, LEDD: Levodopa Equivalent Daily Dose, MDS: Movement Disorders Society, MDT: Munich Dysphagia Test, MoCA: Montreal Cognitive Assessment, PDQ39: Parkinson's Disease Questionnaire, PDSS: Parkinson's Disease Sleep Scale, PIGD: Postural Instabilities and Gait Disorders, RDBSQ: RBD Screening Questionnaire, SAS: Starkstein Apathy Scale, UPDRS: Unified Parkinson's Disease Rating Scale

2.3 Statistical methods

Data analysis was carried out in R, version 4.3.1 [24]. The two-sided Wilcoxon rank-sum test (WRS) and the chi-squared test compared baseline characteristics between men and women (using the "stats" package [24]) on a Bonferroni-corrected 5% level (p-value ≤ 0.05/29 variables). In the longitudinal data, the repeated observations are correlated within the people with PD [25]. Therefore, we applied mixed model analysis [9, 25]. To describe the progression of men and women, we created one model per outcome and sex (using "lmer"-function of the "lme4"-package[26]). Consequently, we performed longitudinal two-level mixed models analyses with disease duration as a fixed effect, a random intercept on participant level and a random slope for disease duration. Further details can be found in Supplement 1. As our aim was to describe the progression, instead of answering causal questions, we only controlled for time to diagnosis and modelled differences between the individuals with the random intercept. Marginal effects of disease duration on the outcomes (i.e., disease duration averaged over random-effects) of the outcomes were estimated with the function "ggpredict" of the R package ggeffects [27] to describe the progression in both groups, illustrated as a plot with the function "plot_model" of the R package sjPlot [28]. As women's ratings of disability differed between self-reported and physician-reported [29], we categorised the results in patient-reported or clinician-assessed outcomes / performance tests. Time, in this case modelled as disease duration, was included in the mixed models to describe progression of the different outcomes (significance tested via t-test). Degree of disability as illustrated in Figure 2 was calculated by the following formula: $Degree\ of\ disability = \left(\frac{Marginal\ effect}{Maximum\ score} \times 100\right)$. For illustrative purposes in Fig. 2, the following scores were inverted to the higher, the worse: Functional Mobility Composite Score (FMCS), Parkinson's Disease Sleep Scale

(PDSS), Montreal Cognitive Assessment (MoCA) and Sniffin' Sticks. Finally the marginal effects were trimmed above the upper and below the lower limit.

3. Results

As illustrated in Figure 1: Flow diagram of recruitment, 957 persons participated in the Luxembourg Parkinson's Study up to the date of data export (22.06.2023). After the exclusion of people with atypical PD, we included 802 people with typical PD with a baseline assessment between 04.03.2015 and 22.06.2023. Figure 1: Flow diagram of recruitment illustrates the flow diagram of recruitment.

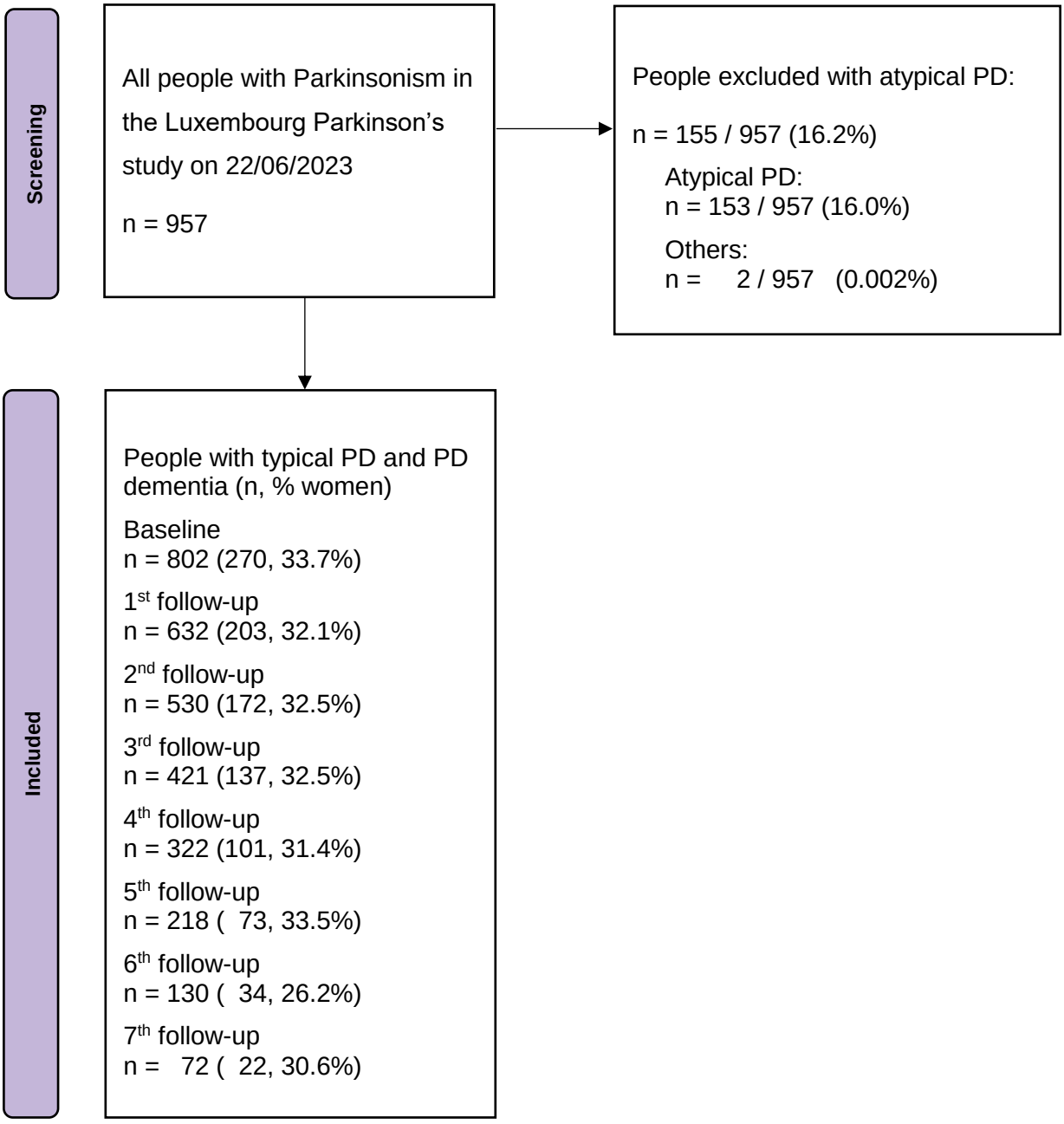

Figure 1: Flow diagram of recruitment

Table 2: Key characteristics

Sample size	802
Data collection period	04.03.2015 – 22.06.2023
Study design	Cohort
Average number of observations	3.0 (3.0)
Setting	People with typical PD living at home or in a nursing home in Luxembourg and the greater region
Inclusion criteria	People with typical PD and PDD
Gender	269 (33.6%) women
Age	68.2 (14.3)
Disease stage	2.0 (0.5)
Outcomes	SAS, BDI-I, FMCS, height (cm), LEDD (mg/kg), MDS-UPDRS I- IV, MDT-PD, MoCA, Sniffin' Sticks, PDQ-39 subscale bodily discomfort, PDQ-39, PDSS, MDS-based PIGD, RBDSQ, MDS-based tremor scale, weight (kg)
Determinants	Disease duration, time to diagnosis

Categorical variables: counts (%), numerical variables: Median (IQR), Abbreviations: PD: Parkinson's disease, PDD: PD dementia, BDI-I: Beck Depression Inventory, FMCS: Functional Mobility Composite Score, LEDD: Levodopa Equivalent Daily Dose, MDS: Movement Disorders Society, MDT: Munich Dysphagia Test, MoCA: Montreal Cognitive Assessment, PDQ39: Parkinson's Disease Questionnaire, PDSS: Parkinson's Disease Sleep Scale, PIGD: Postural Instabilities and Gait Disorders, RBDSQ: RBD Screening Questionnaire, SAS: Starkstein Apathy Scale, UPDRS: Unified Parkinson's Disease Rating Scale

Table 2 summarizes key study characteristics to understand the potential applicability, and thus generalizability of the findings. In the overall cohort at the first clinical assessment, the median age was 68.2 (IQR 14.3) years, and the median age at symptom onset was 61.0 (IQR 18.0) years. The average number of observations was 3.0 (IQR 3.0) and ranged from 1 to 8, with 421 people with PD (52.5%) having 3 or more observations. The median MDS-UPDRS III score was 32.0 (IQR 22.0), and the median Hoehn & Yahr stage was 2.0 (IQR 0.5).

Of the 802 people with typical PD, 269 (33.6%) were women. Table S1 in the Supplement 2 provides a description of the study participants and missing data while the clinical and demographic characteristics of study participants at baseline by sex are presented in Tab. 3. Testing for differences in 29 characteristics at a Bonferroni-corrected 5% level (alpha=0.05/29 = 0.0017), women had significantly worse scores for depression and pain at baseline, while men had worse olfaction scores. In women, the Levodopa Equivalent Daily Dose (LEDD) per kg body weight (mg/ kg) was significantly higher compared to men. Women had significantly less years of

education and experienced a bereavement significantly more often compared to men. We did not test for any differences in weight and height at baseline. We did not identify any statistically significant differences for age, disease duration or time to diagnosis at baseline between men and women with typical PD. Missing data patterns were visually inspected for sociodemographic characteristics and the different outcomes; most variables had missing data for less than 5% of the male and female samples. Rates for missing data were higher for Munich Dysphagia Test-assessed dysphagia (51% and 55% for men and women, respectively).

Table 3: Characteristics of men and women

Variables	Men (N = 532)	Women (N = 270)	p-value
Sociodemographic characteristics			
Age (y)	68.2 (14.5)	68.1 (14.3)	p = 0.3925
Years of education	13.0 (4.0)	12.0 (4.8)	p = 0.0001
Most fluently spoken language			p = 0.7147
Luxembourgish	234 (44.0%)	111 (41.1%)	
French	145 (27.3%)	82 (30.4%)	
German	84 (15.8%)	45 (16.7%)	
Other	69 (13.0%)	31 (11.5%)	
Children (n)	2.0 (2.0)	2.0 (1.0)	p = 0.0085
Marital status			p < 0.0001
Single	20 (3.8%)	24 (8.9%)	
Married / Partnered	442 (83.1%)	164 (60.7%)	
Divorced / Bereaved	67 (12.6%)	80 (29.6%)	
Health-related characteristics			
Diagnosis			p = 0.2049
Typical PD	463 (87.0%)	244 (90.4%)	
PDD	69 (13.0%)	26 (9.6%)	
Hoehn and Yahr (H&Y) Disease Stages			p = 0.3561
H&Y 1	58 (10.9%)	30 (11.1%)	
H&Y 1.5	43 (8.1%)	26 (9.6%)	
H&Y 2	275 (51.7%)	119 (44.1%)	
H&Y 2.5	64 (12.0%)	41 (15.2%)	
H&Y 3	45 (8.5%)	31 (11.5%)	
H&Y 4	27 (5.1%)	13 (4.8%)	
H&Y 5	11 (2.1%)	5 (1.9%)	

Phenotype			p = 0.0040
Tremor dominant	223 (41.2%)	84 (31.1%)	
Intermediate	58 (10.9%)	24 (8.9%)	
PIGD dominant	198 (37.2%)	129 (47.8%)	
Disease duration (y.)	3.1 (5.9)	3.5 (6.6)	p = 0.1079
Age at diagnosis (y.)	63.0 (16.5)	63.0 (17.0)	p = 0.2974
Age at onset of motor-symptoms (y.)	61.0 (18.0)	60.0 (17.2)	p = 0.2121
Time to diagnosis (y.)	1.0 (3.0)	1.0 (3.0)	p = 0.5486
LEDD (mg/kg)	5.5 (6.1)	6.6 (7.7)	p = 0.0008
PDQ-39 (0 – 100)[a]	19.9 (22.4)	25.0 (21.6)	p = 0.0042
Weight (kg)	83.7 (18.7)	65.5 (17.4)	not tested
Height (cm)	173.7 (11.0)	161.0 (9.6)	not tested
Non-motor symptoms			
MoCA (0 – 30)[b]	25.0 (5.0)	26.0 (5.0)	p = 0.0123
BDI-I (0 – 63)[a]	8.0 (9.0)	10.0 (9.0)	p = 0.0002
SAS (0 - 42)[a]	13.0 (7.0)	13.0 (7.0)	p = 0.3345
Sniffin' Sticks (0 - 16)[b]	8.0 (5.0)	9.0 (4.0)	p < 0.0001
PDQ-39 subscale bodily discomfort (0 – 100)[a]	25.0 (33.3)	41.7 (41.7)	p = 0.0001
PDSS (0 - 150)[b]	110.0 (34.0)	106.5 (36.1)	p = 0.0198
RBDSQ (0 - 13)[a]	4.0 (5.0)	4.0 (4.0)	p = 0.1777
MDS-UPDRS I (0 – 52)[a]	9.0 (8.0)	10.0 (9.0)	p = 0.0118
Motor symptoms			
MDS-UPDRS II (0 – 52)[a]	10.0 (10.0)	9.0 (10.0)	p = 0.7435
MDS-UPDRS III (0 – 132)[a]	33.0 (21.0)	31.0 (23.8)	p = 0.1936
MDS-UPDRS IV (0 – 24)[a]	0.0 (0.0)	0.0 (2.5)	p = 0.1724
FMCS (0 – 100)[b]	81.2 (31.2)	76.6 (34.4)	p = 0.0378
PIGD Score (0 – 20)[a]	2.0 (4.0)	3.0 (4.0)	p = 0.0617
Tremor Scale (0 - 4)[a]	0.5 (0.6)	0.5 (0.6)	p = 0.0294
MDT Score (3 - 103)[a]	6.0 (9.0)	6.0 (7.8)	p = 0.4668

Categorical variables: counts (%), numerical variables: median (IQR), a : Greater = worse, b : Greater = better, numerical variables : two-sided Wilcoxon rank-sum test, categorical variables : chi-squared test, Abbreviations: BDI-I: Beck Depression Inventory I, FMCS: Functional Mobility Composite Score, LEDD: Levodopa Equivalent Daily Dose, MDS: Movement Disorders Society, MDT: Munich Dysphagia Test, MoCA: Montreal Cognitive Assessment, PDQ39: Parkinson's Disease Questionnaire, PDSS: Parkinson's Disease Sleep Scale, PIGD: Postural Instabilities and Gait Disorders, RBDSQ: RBD Screening Questionnaire, SAS: Starkstein Apathy Scale, UPDRS: Unified Parkinson's Disease Rating Scale

While many outcomes showed a linear trajectory, this was not the case for apathy (m (men)), global cognition (m), depression (m), weight, pain (m), quality of sleep (m), patient-reported motors symptoms (m), motor complications (w (women)), postural instability and gait disturbances (PIGD), tremor (m), LEDD and health-related quality

of life (w) where a quadratic time component fitted best as adding the quadratic effect significantly improved the fit. As expected from a chronic progressive disorder, people with typical PD showed a significant progression (Bonferroni-corrected 5% level (alpha=0.05/15 = 0.0033)) in eleven of fifteen outcomes. The outcomes showing no significant progression were pain, RBD, quality of sleep and postural instabilities and gait disturbances in women, while tremor did not significantly decrease in men or women. We described the progression for each motor- and non-motor symptom in men and women in Tab. 4 and illustrated the progression (marginal effects converted to % impairment) of both groups in Figure 2. The progression of the secondary outcomes (weight, height, health-related quality of life and LEDD) and all coefficients of the longitudinal mixed-models can be found in the Supplement 2 and the detailed figures per symptom for clinical interpretation in the Supplement 3.

Women mostly demonstrated a slower progression than men. More specifically, as described in Table 4 and illustrated in Figure 2, women had a slower progression in cognition and apathy. Thus, women's confidence intervals in apathy and cognition didn't overlap anymore with men's confidence intervals after twenty years of disease duration (m: 21.0 (95%CI: 19.1, 22.9), w: 16.1 (95%CI: 14.4, 17.8)). Moreover, the marginal effects of the MoCA score after 20 years of disease duration in men were 16.7 (95%CI: 14.9, 18.5) while women still had a score of 23.0 (21.8, 24.2) with a non-linear (quadratic) progression in men. Concerning the progression of impaired sleep, we observed neither a significant worsening in quality of sleep nor in RBD in women, while both symptoms progressed significantly in men (Table 4, Figure 2). Finally, in women we observed a faster progression of bodily discomfort compared to men. Thus, in women, bodily discomfort continuously worsened, while in men it stabilized after 20 years. After worse depression scores for women at baseline, both

groups had similar depression scores after 20 years of disease duration (m : 16.2 (95% CI: 13.7, 18.6), w: 15.7 (95%CI: 13.6, 17.8)) in line with the non-linear (quadratic) progression in men. In women we observed a faster worsening of motor complications in early PD but motor complications in women stabilized and even decreased with advanced disease duration, while in men we observed a linear progression. In men and women we observed similar progression for MDS-UPDRS I and olfaction (Table 4, Figure 2).

As further described in Tab. 4 and illustrated in Fig. 2, in motor symptoms, we observed greater values for patient-reported motor symptoms at 10 years disease duration in men compared to women. Similarly, in women, we observed a 18.9% slower progression of clinical-assessed motor symptoms (points / year of disease duration) compared to men (m (men): +1.27 (95%CI: 1.03, 1.51), w (women): +1.07 (95%CI: 0.76, 1.38)). We observed 27.9 % slower progression of patient-reported functional mobility per year of disease duration in women (m: -2.58 (95%CI: -2.96, -2.12), w: -1.86 (95%CI: -2.29 -1.43). In women, we also observed worse PIGD scores after 20 years of disease duration (10.9, 95%CI: 9.1, 12.6) compared to men (14.3, 95%CI: 12.8, 15.9). In both groups, we observed similar progression for dysphagia (m: +0.734 (95%CI: 0.557, 0.910), w: +0.761 (95%CI: 0.514, 1.008)). While we did not measure a significant change in women's tremor, it significantly improved in men (-0.010, 95%CI: 0.017, 0.004).

In the secondary outcomes, we observed a reversed u-shaped progression in men in LEDD per kilogram body weight, while in women we observed a linear increase in the LEDD per kilogram. In women, we observed a slower linear decrease in health-related quality of life, while in men we observed a faster and non-linear (i.e., quadratic) progression (Fig. S1 and S2, Tab. S2).

While in women, after controlling for age, the MoCA did not significantly progress, the other findings were independent of age and time to diagnosis. The longer the time from first symptoms to the diagnosis of typical PD, the worse the RBD in men ($p = 0.015$) and tremor in women ($p < 0.001$) (Tab. S4 and S5 in Supplement 2). Finally, the frequency of missing data at follow-up in women was not significantly higher than in men.

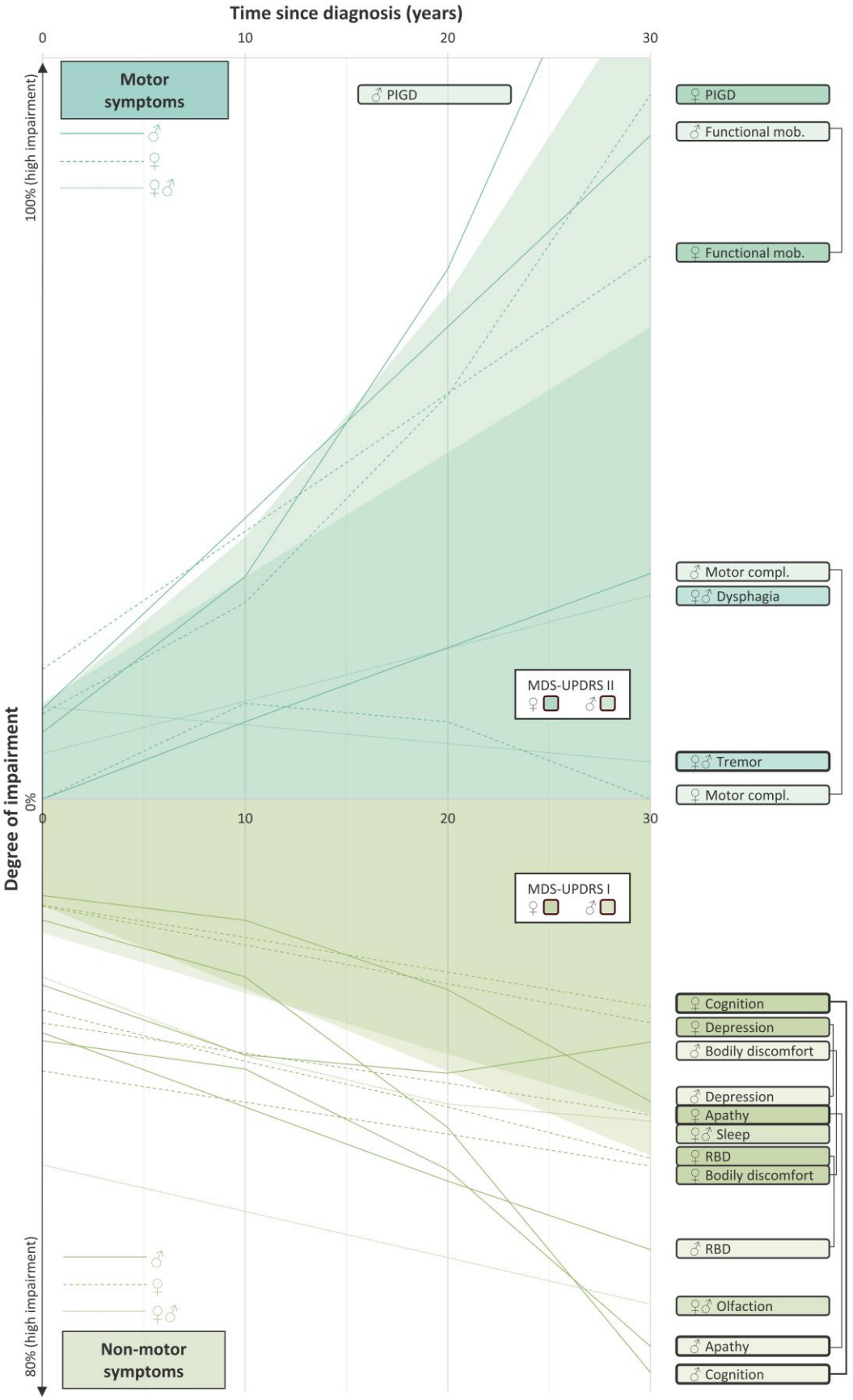

Figure 2: Progression of motor- and non-motor symptoms in men and women with typical PD and PDD. Degree of impairment = 0 – 100% (greater = worse). Abbreviations: PD: Parkinson's disease, PDD: PD dementia, PIGD: Postural Instabilities and Gait Disturbances, RBD: Rapid Eye Movement (REM) Behavior Disorder

Table 4: Progression for patient-reported & clinician-assessed outcomes and performance tests

Patient-reported outcomes

DD	**Apathy** SAS (0 - 42)[a]		**Depression** BDI-I (0 – 63)[a]		**Dysphagia** MDT-PD (3 – 103)[a]	
	m	w	m	w	m	w
0	13.7 (13.0, 14.5)	12.7 (11.8, 13.6)	8.2 (7.2, 9.1)	9.1 (7.9, 10.2)	6.3 (5.1, 7.5)	6.5 (4.7, 8.2)
10	15.3 (14.6, 15.9)	14.4 (13.6, 15.2)	10.3 (9.6, 11.1)	12.4 (11.4, 13.4)	13.6 (12.4, 14.8)	14.1 (12.2, 15.9)
20	21.0 (19.1, 22.9)	16.1 (14.4, 17.8)	16.2 (13.7, 18.6)	15.7 (13.6, 17.8)	20.9 (18.2, 23.7)	21.7 (17.8, 25.6)
30	31.0 (25.9, 36.1)	17.9 (15.1, 20.6)	25.7 (19.0, 32.3)	19.0 (15.6, 22.4)	28.3 (23.8, 32.7)	29.3 (23.1, 35.5)
40	45.2 (34.9, 55.5)	-	38.8 (25.4, 52.2)	-	35.6 (29.4, 41.8)	-

DD	**Functional mobility** FMCS (0 – 100)[b]		**Non-motor symptoms** MDS-UPDRS I (0 – 52)[a]		**Patient-reported motor symptoms** MDS-UPDRS II (0 – 52)[a]	
	m	w	m	w	m	w
0	87.8 (85.7, 90.0)	82.5 (79.2, 85.8)	7.5 (6.8, 8.2)	9.4 (8.4, 10.5)	6.4 (5.6, 7.3)	6.8 (5.8, 7.9)
10	62.1 (59.1, 65.0)	63.9 (60.5, 67.3)	13.3 (12.6, 14.0)	13.6 (12.7, 14.6)	18.4 (17.2, 19.5)	15.6 (14.3, 16.8)
20	36.3 (29.9, 42.7)	45.3 (38.4, 52.3)	19.1 (17.5, 20.7)	17.9 (15.9, 19.8)	35.4 (32.2, 38.6)	24.3 (21.8, 26.8)
30	10.5 (0.4, 20.6)	26.8 (15.8, 37.8)	25.0 (22.4, 27.5)	22.1 (19.0, 25.2)	57.5 (49.7, 65.2)	33.1 (29.2, 37.0)
40	-15.3 (-29.2, -1.5)	-	30.8 (27.2, 34.4)	-	84.6 (69.7, 99.5)	-

DD	**Pain** PDQ-39 subscale bodily discomfort (0 - 100)[a]		**RBD** RBDSQ (0 – 13)[a]		**Quality of sleep** PDSS (0 – 150)[b]	
	m	w	m	w	m	w
0	25.1 (22.4, 27.8)	36.7 (32.7, 40.6)	4.1 (3.7, 4.5)	3.7 (3.3, 4.2)	114.0 (111.2, 116.9)	105.6 (101.6, 109.6)
10	34.5 (32.3, 36.7)	40.9 (38.0, 43.9)	5.4 (5.0, 5.7)	4.6 (4.2, 5.0)	98.1 (95.8, 100.3)	99.0 (95.8, 102.1)
20	37.0 (31.2, 42.9)	45.2 (39.4, 51.0)	6.7 (6.0, 7.4)	5.4 (4.5, 6.4)	88.3 (83.6, 93.1)	92.3 (85.9, 98.7)
30	32.8 (16.4, 49.1)	49.5 (39.9, 59.0)	7.9 (6.8, 9.1)	6.3 (4.8, 7.8)	84.8 (71.5, 98.1)	85.7 (75.2, 96.1)
40	21.7 (-11.8, 55.2)	-	9.2 (7.7, 10.8)	-	87.5 (59.6, 115.5)	-

Clinician-assessed outcomes and performance tests

DD	**Cognition** MoCA Score (0 – 30)[b]				**Clinician-Assessed motor symptoms** MDS-UPDRS III (0 – 132)[a]		**Motor complications** MDS-UPDRS IV (0 – 24)[a]	
	m			w	m	w	m	w
		Age adj.		Age adj.				
0	25.1 (24.6, 25.6)	24.8 (24.3, 25.2)	25.7 (25.2, 26.2)	25.4 (24.8, 25.9)	30.0 (28.4, 31.6)	26.9 (25.0, 28.9)	0.0 (-0.2, 0.3)	-0.2 (-0.7, 0.3)
10	22.8 (22.2, 23.4)	23.7 (23.2, 24.2)	24.4 (23.7, 25.0)	24.7 (24.1, 25.3)	42.7 (41.0, 44.5)	37.6 (35.5, 39.8)	2.5 (2.1, 2.8)	3.1 (2.6, 3.6)
20	16.7 (14.9, 18.5)	20.0 (18.3, 21.7)	23.0 (21.8, 24.2)	24.1 (22.8, 25.4)	55.5 (51.6, 59.3)	48.3 (43.7, 52.9)	4.9 (4.1, 5.6)	2.5 (0.9, 4.1)

30	6.8 (2.1, 11.4)	13.6 (9.1, 18.0)	21.6 (19.7, 23.6)	23.4 (21.4, 25.5)	68.2 (62.1, 74.4)	59.0 (51.7, 66.3)	7.3 (6.1, 8.5)	-2.0 (-6.5, 2.6)
40	-	-	-	-	80.9 (72.4, 89.4)	-	-	-

DD	**Olfaction** Sniffin' Sticks (0 – 16)[b]		**Postural Instabilities and Gait Disturbances** MDS-UPDRS based PIGD score (0 - 20)[a]		**Tremor** MDS-UPDRS based tremor scale (0 – 4)[a]	
	m	w	m	w	m	w
0	8.1 (7.7, 8.4)	9.4 (8.9, 9.9)	1.8 (1.4, 2.1)	2.3 (1.8, 2.9)	0.6 (0.6, 0.7)	0.5 (0.5, 0.6)
10	7.1 (6.8, 7.3)	8.2 (7.8, 8.6)	6.0 (5.5, 6.5)	5.3 (4.6, 5.9)	0.5 (0.5, 0.6)	0.4 (0.4, 0.5)
20	6.1 (5.6, 6.6)	6.9 (6.1, 7.7)	14.3 (12.8, 15.9)	10.9 (9.1, 12.6)	0.4 (0.3, 0.5)	0.3 (0.1, 0.5)
30	5.1 (4.3, 6.0)	5.7 (4.4, 7.0)	26.5 (22.5, 30.5)	19.0 (14.6, 23.4)	0.3 (0.2, 0.5)	0.2 (-0.2, 0.7)
40	-	-	42.7 (35.0, 50.4)	-	0.2 (-0.0, 0.4)	

[a] Greater = Worse, [b] Greater = Better, Abbreviations: DD = Disease duration, Outcome marginal effect (95% CI), BDI-I: Beck Depression Inventory, FMCS: Functional Mobility Composite Score, LEDD: Levodopa Equivalent Daily Dose, MDS: Movement Disorders Society, MDT: Munich Dysphagia Test, MoCA: Montreal Cognitive Assessment, PDQ39: Parkinson's Disease Questionnaire, PDSS: Parkinson's Disease Sleep Scale, PIGD: Postural Instabilities and Gait Disorders, RBDSQ: RBD Screening Questionnaire, SAS: Starkstein Apathy Scale, UPDRS: Unified Parkinson's Disease Rating Scale

4. Discussion

The present study described and illustrated the progression of motor- and non-motor symptoms in men and women with typical PD. Both men and women showed a progression (i.e., deterioration) in all symptoms except tremors. Comparing symptoms progression between men and women, women had worse symptoms for depression and pain at baseline and experienced a slower progression in cognition, apathy, quality of sleep and self-reported disability. However, this was not the case for bodily discomfort or depression for which women's starting levels were lower and symptoms progressed faster compared to men. Conversely, both groups had similar apathy scores at baseline and we observed a faster progression for men, exceeding women after twenty years. While motor complications in women progressed faster in the first ten years and stabilized after that, this was not the case for men. Interestingly, tremors improved in both men and women. We observed similar trajectories for patient-reported outcomes compared to clinician-assessed outcomes in both men and women.

Non-motor symptoms

Previous reviews [2-4] discussed the heterogeneous findings of sex-specific progression of PD. According to our findings, women tended to have a generally slower disease progression than men, with the exceptions of bodily discomfort and depression. However, in our study, women had worse bodily discomfort at baseline similarly to previous findings [29-32]. Additionally, women's bodily discomfort worsened over time, while men's scores remained rather stable. This may be due to different symptom expressions, such as the restless legs syndrome being more common and severe in women [32]. Also, in women, depression was worse at baseline with a faster progression in early PD (first ten years of disease duration), but both groups showed

similar average scores after twenty years of disease duration similar to previous research [33].

Our study confirmed that women were less likely to decline in cognitive performance over time [34]. Moreover, we observed a similar progression of apathy, a feature of PD dementia [35]. Thus, both groups had similar apathy scores at baseline and we observed a faster worsening for men, exceeding women after 20 years. While both groups had similar RBD symptoms at baseline [36], women tended to have a slower progression in RBD symptoms than men. Similarly, in women we observed a worse quality of sleep at baseline and a slower progression with similar scores after ten years of disease duration. Finally, in both groups we observed a similar progression of dysphagia and olfaction, while men had worse olfaction at baseline. This can be explained by the olfactory superiority in women[37].

Motor symptoms

Our results support previous longitudinal findings [33, 34] of women having higher disability scores at baseline, but men progressing faster. While female's motor complications tended to increase faster at the beginning, they stabilized and decreased over time. Additionally, we did not detect any differences in the motor complications (MDS-UPDRS IV) while in women the mg/kg LEDD dose was significantly higher compared to men. However, women tended to have a slower progression of MDS-UPDRS III supporting previous findings [33]. Our results also confirm previous findings [5] that the PIGD dominant phenotype is more frequent in women. While women tended to have worse patient-reported functional mobility (FMCS) at baseline, we observed a 27.1% slower FMCS progression in women compared to men. Interestingly, for both groups the score for tremor (MDS-based combination of MDS-UPDRS II & III) improved over the years while the changes were

not significant for women. This is in line with previous findings [38] describing unstable motor subtypes over time and a qualitative study [39], in which tremor was decreasingly reported as the condition progressed. However, the biological plausibility for these findings needs to be investigated by future research. Finally, both groups appear to have a similar progression in dysphagia.

Secondary outcomes

We observed relevant drug dosage discrepancies between men and women. Specifically, in women we assessed a higher mg/kg LEDD compared to men at baseline. Also, in women we observed a linear increase of LEDD mg/kg compared to men with a reversed u-shaped relationship with a decreasing mg/kg at an advanced PD duration. Thus, in women, due to differences in levodopa metabolism and a higher LEDD (mg/kg) the risk for levodopa-related motor complications is elevated [2, 5, 40]. However, in women, we observed a reversed u-shaped relationship (i.e., a faster increase) in motor complications (MDS-UPDRS IV) in early PD decreasing after the first ten years compared to men with a linear increase of motor complications. As reported in the Supplement 2, while women tended to have worse health-related quality of life at baseline, they also had a slower progression of health-related quality of life, an observation in line with a previous longitudinal study [41]. Also, male sex was associated with camptocormia, i.e., abnormal severe forward flexion of the trunk while standing or walking in a previous study [42]. However, our study did not confirm this finding. Accordingly, in women, after twenty years of disease duration, they lost 10.6% of their initial height, while men lost only 3.6%. We did not observe greater weight loss in women, nor a faster progression in dysphagia. Interestingly, the time to diagnosis was not significantly different in men and women. This is surprising, as women with PD tend to be older than men at time of diagnosis [43].

Strengths and limitation

This study has some strengths and limitations. For instance, we enhanced the generalizability of our findings by analysing data of all participants of the Luxembourg Parkinson's study including people with PD or PDD from Luxembourg and the Greater Region, who were treated and lived in varying settings and environments. More specifically, the range of people with PD was broad, including men and women from 22 to 92 years with 1 to 30 years of education, living from 0 to 32 years with the disease and speaking different languages. 68.7% of the people with PD were in disease stages H&Y 1 – 2, the disease stages ranged from H&Y 1 to H&Y 5. Moreover, we used advanced statistical methodology to estimate changes over time in our longitudinal dataset with mixed models taking into account correlations of the observations. Although our analysis is observational, our longitudinal study provided a comprehensive description of the individual progression of symptoms in Parkinson's disease while previous studies were mainly cross-sectional analyses with some exceptions [33, 41, 44, 45]. The COVID-19 pandemic and deaths since baseline assessment (101, 12.6%) may have led to missing data. For the MDT score we noted higher rates of missing values, as it was added later during the study explaining the nature of the missing values. Nevertheless, the analyses on this outcome should be considered exploratory. Despite the potential sampling bias for the analyses involving the onsite test MDS-UPDRS III, the frequency of missing data at follow-up was similar in both groups. Consequently, the observed differences in progression are probably not due to data missing not at random between men and women. Data collection standards have been developed to minimise missing data and information bias.

Our research described the progression since the diagnosis. Future research should use data of risk and prodromal cohorts to describe the biological progression before the diagnosis of PD [46]. Also, protective factors in women, especially for global cognition, should be further explored. Moreover, the biological plausibility for the sex-specific progression of cognition in PD needs to be investigated by future research. Sex-specific interventions to prevent cognitive decline and apathy in men, as well as bodily discomfort and depression in women need to be developed by research, while health-professionals should proactively monitor and offer interventions. Moreover, different symptom expressions in women compared to men need to be further investigated.

In conclusion, our study provided a comprehensive data-based description and illustration of the clinical progression of motor- and non-motor symptoms associated with Parkinson's disease for men and women. Moreover, the detailed figures in the Supplement 3 should aid interpretation by health professionals. Unexpected findings like the improvement of tremor over time and factors explaining the resilience in women with PD especially in cognition, apathy, quality of sleep and MDS-UPDRS II need to be explored further. To enhance well-being and personalised treatment in PD, we recommend considering a sex-specific approach to managing PD symptoms.

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Geeta ACHARYA 2, Gloria AGUAYO 2, Myriam ALEXANDRE 2, Muhammad ALI 1, Wim AMMERLANN 2, Giuseppe ARENA 1, Rudi BALLING 1, Michele BASSIS 1, Katy BEAUMONT 2, Regina BECKER 1, Camille BELLORA 2, Guy BERCHEM 3, Daniela BERG 11, Alexandre BISDORFF 5, Ibrahim BOUSSAAD 1, Kathrin BROCKMANN 11, Jessica CALMES 2, Lorieza CASTILLO 2, Gessica CONTESOTTO 2, Nico DIEDERICH 3, Rene DONDELINGER 5, Daniela ESTEVES 2, Guy FAGHERAZZI 2, Jean-Yves FERRAND 2, Manon GANTENBEIN 2, Thomas GASSER 11, Piotr GAWRON 1, Soumyabrata GHOSH 1, Marijus GIRAITIS 2,3, Enrico GLAAB 1, Elisa GÓMEZ DE LOPE 1, Jérôme GRAAS 2, Mariella GRAZIANO 17, Valentin GROUES 1, Anne GRÜNEWALD 1, Wei GU 1, Gaël HAMMOT 2, Anne-Marie HANFF 2, 20, 21, Linda HANSEN 1,3, Michael HENEKA 1, Estelle HENRY 2, Sylvia HERBRINK 6, Sascha HERZINGER 1, Michael HEYMANN 2, Michele HU 8, Alexander HUNDT 2, Nadine JACOBY 18, Jacek JAROSLAW LEBIODA 1, Yohan JAROZ 1, Sonja JÓNSDÓTTIR 2, Quentin KLOPFENSTEIN 1, Jochen KLUCKEN 1,2,3, Rejko KRÜGER 1,2,3, Pauline LAMBERT 2, Zied LANDOULSI 1, Roseline LENTZ 7, Inga LIEPELT 11, Robert LISZKA 14, Laura LONGHINO 3, Victoria LORENTZ 2, Paula Cristina LUPU 2, Tainá M. MARQUES 1, Clare MACKAY 10,

Walter MAETZLER 15, Katrin MARCUS 13, Guilherme MARQUES 2, Patricia MARTINS CONDE 1, Patrick MAY 1, Deborah MCINTYRE 2, Chouaib MEDIOUNI 2, Francoise MEISCH 1, Myriam MENSTER 2, Maura MINELLI 2, Michel MITTELBRONN 1,4, Brit MOLLENHAUER 12, Friedrich MÜHLSCHLEGEL 4, Romain NATI 3, Ulf NEHRBASS 2, Sarah NICKELS 1, Beatrice NICOLAI 3, Jean-Paul NICOLAY 19, Fozia NOOR 2, Marek OSTASZEWSKI 1, Clarissa P. C. GOMES 1, Sinthuja PACHCHEK 1, Claire PAULY 1,3, Laure PAULY 2, 20, Lukas PAVELKA 1,3, Magali PERQUIN 2, Rosalina RAMOS LIMA 2, Armin RAUSCHENBERGER 1, Rajesh RAWAL 1, Dheeraj REDDY BOBBILI 1, Kirsten ROOMP 1, Eduardo ROSALES 2, Isabel ROSETY 1, Estelle SANDT 2, Stefano SAPIENZA 1, Venkata SATAGOPAM 1, Margaux SCHMITT 2, Sabine SCHMITZ 1, Reinhard SCHNEIDER 1, Jens SCHWAMBORN 1, Amir SHARIFY 2, Ekaterina SOBOLEVA 1, Kate SOKOLOWSKA 2, Hermann THIEN 2, Elodie THIRY 3, Rebecca TING JIIN LOO 1, Christophe TREFOIS 1, Johanna TROUET 2, Olena TSURKALENKO 2, Michel VAILLANT 2, Mesele VALENTI 2, Gilles VAN CUTSEM 1,3, Carlos VEGA 1, Liliana VILAS BOAS 3, Maharshi VYAS 1, Richard WADE-MARTINS 9, Paul WILMES 1, Evi WOLLSCHEID-LENGELING 1, Gelani ZELIMKHANOV 3

1 Luxembourg Centre for Systems Biomedicine, University of Luxembourg, Esch-sur-Alzette, Luxembourg

2 Luxembourg Institute of Health, Strassen, Luxembourg

3 Centre Hospitalier de Luxembourg, Strassen, Luxembourg

4 Laboratoire National de Santé, Dudelange, Luxembourg

5 Centre Hospitalier Emile Mayrisch, Esch-sur-Alzette, Luxembourg

6 Centre Hospitalier du Nord, Ettelbrück, Luxembourg

7 Parkinson Luxembourg Association, Leudelange, Luxembourg

8 Oxford Parkinson's Disease Centre, Nuffield Department of Clinical Neurosciences, University of Oxford, Oxford, UK

9 Oxford Parkinson's Disease Centre, Department of Physiology, Anatomy and Genetics, University of Oxford, South Parks Road, Oxford, UK

10 Oxford Centre for Human Brain Activity, Wellcome Centre for Integrative Neuroimaging, Department of Psychiatry, University of Oxford, Oxford, UK

11 Center of Neurology and Hertie Institute for Clinical Brain Research, Department of Neurodegenerative Diseases, University Hospital Tübingen, Germany

12 Paracelsus-Elena-Klinik, Kassel, Germany

13 Ruhr-University of Bochum, Bochum, Germany

14 Westpfalz-Klinikum GmbH, Kaiserslautern, Germany

15 Department of Neurology, University Medical Center Schleswig-Holstein, Kiel, Germany

16 Department of Neurology Philipps, University Marburg, Marburg, Germany

17 Association of Physiotherapists in Parkinson's Disease Europe, Esch-sur-Alzette, Luxembourg

18 Private practice, Ettelbruck, Luxembourg

19 Private practice, Luxembourg, Luxembourg

20 Faculty of Science, Technology and Medicine, University of Luxembourg, Esch-sur-Alzette, Luxembourg

21 Department of Epidemiology, CAPHRI School for Public Health and Primary Care, Maastricht University Medical Centre+, Maastricht, the Netherlands

Author roles

A-MH: 1A-C, 2A-B, 3A

CMC: 1A-C, 2C, 3A-B

AR: 1A, 2A-C, 3B

GA: 3B

MZ, AKL: 1A, 2A, 2C, 3B

RK: 1A-B, 2A, 2C, 3B

Detailed author roles

A-MH: Conceptualization, Methodology, Formal analysis, Investigation, Visualization, Project administration, Writing – original draft, Writing – review & editing.

CMC: Conceptualization, Methodology, Supervision, Writing – original draft, Writing – review & editing.

AR: Methodology, Formal analysis, Writing – review & editing.

GA: Methodology, Writing – review & editing.

CP, SJ, OT: Investigation, writing – review & editing.

MZ, AKL: Conceptualization, Methodology, Supervision, Writing – review & editing.

RK: Conceptualization, Methodology, Funding, Resources, Supervision, Writing – review & editing.

All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Ethical Compliance Statement

The studies involving human participants were reviewed and obtained a positive opinion from the National Ethics Board (CNER Ref: 201407/13). The patients/participants provided their written informed consent to participate in this study. 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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Supplementary material

1. Modelling the linear development over time

After **adding the** random intercept on subject-level to describe the importance to cluster the repeated observations within the subjects[1] we **evaluated whether a random slope for time was necessary** by performing a likelihood ratio test[2] (using “anova”-function of the “lme4”-package[26], method = “lrt”) to compare the model with[3] and without[2] a random slope for time, i.e., disease duration. After modelling the linear development over time, we extended the fixed effects with a quadratic time component, i.e. time[2 5]. To evaluate whether or not a second-order polynomial should be used to describe the longitudinal development over time, we performed a likelihood ratio test[6] (using “anova”-function of the “lme4”-package [26], method = “lrt”) to compare the model with[5] and without[4] quadratic time component.

[1] model_1 <- lme4::lmer(outcome~disease_duration+(1|ND), REML = FALSE, data=reduced_data)
[2] anova(model_1, model_2)
[3] model_2 <- lme4::lmer(outcome~disease_duration+(1+disease_duration|ND), REML = FALSE, data=reduced_data)
[5] model_3 <- lme4::lmer(outcome~disease_duration+I(disease_duration^2)+(1+disease_duration|ND), REML = FALSE, data=reduced_data)
[6] anova(model_2, model_3)

2. Supplementary tables

Table S1: Characteristics of the study participants at baseline (N = 802) incl. numbers of missing data for each variable of interest

Characteristics	Mean (SD) / n (%)	Min. - Max.	Median (Pct25-75)	Missing N (%)
Sociodemographic characteristics				
Age (y.)	67.1 (10.9)	22.0 – 92.9	68.2 (60.2 – 74.5)	1 (0.1%)
Female Sex	270 (33.7%)			0 (0.0%)
Years of Education	13.0 (4.1)	1.0 – 30.0	13.0 (10.0 - 16.0)	9 (1.1%)
Language most fluent				1 (0.1%)
French	227 (28.3%)			
German	129 (16.1%)			
Luxembourgish	345 (43.0%)			
Other	100 (12.5%)			
Marital status				5 (0.6%)
Single	44 (5.5%)			
Married / Partnered	606 (75.6%)			
Divorced / Bereaved	147 (18.3%)			
Health-related characteristics				
PD Diagnosis	707 (88.2%)			0 (0%)
Hoehn & Yahr (H&Y) Disease Stages				14 (1.7%)
H&Y 1	88 (11.0%)			
H&Y 1.5	69 (8.6%)			
H&Y 2	394 (49.1%)			
H&Y 2.5	105 (13.1%)			
H&Y 3	76 (9.5%)			
H&Y 4	40 (5.0%)			
H&Y 5	16 (2.0%)			
Disease Duration (y.)	5.0 (5.1)	0.0 – 32.3	3.2 (1.1 - 7.4)	54 (6.7%)
LEDD (mg.)	493.4 (400.4)	0.0 – 2062.0	400.0 (200.0 – 712.8)	24 (3.0%)
LEDD (mg./kg.)	7.3 (5.4)	0.0 – 36.9	5.8 (3.6 – 10.0)	34 (4.2%)
Time to Diagnosis (y.)	2.7 (5.1)	-1.0 – 46.0	1.0 (0.0 – 3.0)	30 (3.7%)
Weight (kg)	79.2 (16.4)	40.1 – 153.0	78.5 (67.7 – 89.4)	21 (2.6%)
Height (cm)	169.3 (9.7)	137.0 – 205.0	169.1 (162.2 – 176.2)	25 (3.1%)
Non-motor symptoms				
MoCA (0 – 30)[b]	24.6 (4.2)	5.0 – 30.0	25.0 (23.0 - 28.0)	22 (2.7%)
BDI-I (0 – 63)[a]	9.8 (7.3)	0.0 – 51.0	8.0 (5.0 - 14.0)	46 (5.7%)
SAS (0 - 42)[a]	14.0 (5.9)	1.0 – 36.0	13.0 (10.0 – 17.0)	54 (6.7%)
PDQ-39 (0 – 100)[a]	24.6 (17.3)	0.0 – 82.1	21.8 (10.9 – 34.6)	69 (8.6%)
MDT Score (3 - 103)[a]	8.7 (9.2)	0.0 – 56.0	6.0 (3.0 – 11.0)	375 (46.8%)
Sniffin' Sticks (0 - 16)[b]	8.1 (3.2)	1.0 – 16.0	8.0 (6.0 – 10.0)	60 (7.5%)

PDQ-39 Subscale Bodily Discomfort (0 – 100)[a]	33.2 (23.9)	0.0 – 100	33.3 (16.7 – 50.0)	44 (5.5%)
PDSS (0 - 150)[b]	105.4 (24.9)	17.0 – 150.0	108.4 (90.3 – 125.0)	59 (7.4%)
RBDSQ (0 - 13)[a]	4.5 (3.2)	0.0 – 13.0	4.0 (2.0 – 7.0)	64 (8.0%)
MDS-UPDRS I (0 – 52)[a]	10.4 (6.9)	0.0 – 39.0	9.0 (5.0 - 14.0)	33 (4.1%)
Motor symptoms				
MDS-UPDRS II (0 – 52)[a]	11.0 (8.4)	0.0 – 48.0	9.0 (5.0 - 15.0)	24 (3.0%)
MDS-UPDRS III (0 – 132)[a]	34.1 (16.7)	0.0 – 100.0	32.0 (22.0 - 44.0)	21 (2.6%)
MDS-UPDRS IV (0 – 24)[a]	1.6 (3.2)	0.0 – 16.0	0.0 (0.0 - 1.0)	17 (2.2%)
FMCS (0 – 100)[b]	74.6 (23.0)	0.0 – 100.0	81.2 (60.9 - 93.8)	46 (5.7%)
PIGD Score (0 – 20)[a]	3.5 (3.8)	0.0 – 20.0	2.0 (1.0 – 5.0)	25 (3.1%)
Tremor Scale (0 - 4)[a]	0.6 (0.4)	0.0 – 2.4	0.5 (0.3 – 0.8)	21 (2.6%)

Note. [a] *Greater = Worse,* [b] *Greater = Better*

Table S2: Progression of secondary outcomes

Disease duration	**A** PDQ-39 (0 – 100)[a]		**B** Weight (kg.)		**C** Height (cm.)		**D** LEDD (mg.)		**E** LEDD (mg./kg.)	
	Men	**Women**	**Men**	**Women**	**Men**	**Women**	**Men**	**Women**	**Men**	**Women**
0	16.7 (14.7, 18.6)	21.0 (18.5, 23.5)	85.2 (83.6, 86.6)	68.3 (65.7, 70.9)	174.6 (173.9, 175.4)	161.9 (160.9, 162.9)	214.0 (176.4, 251.7)	223.8 (172.8, 274.9)	2.9 (2.3, 3.4)	4.6 (3.9, 5.3)
10	31.6 (29.5, 33.7)	31.6 (29.1, 34.1)	84.1 (82.4, 85.7)	67.7 (65.6, 69.9)	171.5 (170.8, 172.3)	159.3 (158.2, 160.4)	886.6 (841.5, 931.7)	822.3 (763.1, 881.5))	10.8 (10.1, 11.5)	11.9 (10.8, 13.0)
20	52.0 (45.7, 58.3)	42.3 (37.3, 47.3)	78.0 (73.5, 82.5)	61.0 (55.1, 67.0)	168.4 (167.1, 169.7)	156.7 (154.7, 158.6)	1055.0 (907.4, 1202.7)	1059.2 (889.2, 1229.1)	12.7 (10.0, 15.3)	19.2 (16.8, 21.6)
30	77.9 (62.1, 93.6)	52.9 (45.0, 60.8)	66.9 (55.5, 78.3)	48.3 (32.7, 63.8)	165.3 (163.3, 167.3)	154.1 (151.1, 157.0)	719.4 (338.2, 1100.5)	934.4 (484.4, 1384.5)	8.5 (1.6, 15.5)	26.6 (22.8, 30.3)
40	109.2 (78.7, 139.7)	-	-	-	-	-	-120.5 (-867.8, 626.8)	-	-	-

Note. Marginal effect (95% CI), [a] Greater = Worse

Table S3: Fixed effects of secondary outcomes in men and women

	Height (cm.)				**Weight (kg.)**				**PDQ-39**[a] (0 – 100)				**LEDD (mg)**				**LEDD (mg / kg)**			
	Men		**Women**		**Men**		**Women**		**Men**		**Women**		**Men**		**Women**		**Men**		**Women**	
Independent variables	B (CI 95%)	p-values	B (CI 95%)	p-values	B (CI 95%)	p-values	B (CI 95%)	p-values	B (CI 95%)	p-values	B (CI 95%)	p-values	B (CI 95%)	p-values	B (CI 95%)	p-values	B (CI 95%)	p-values	B (CI 95%)	p-values
Intercept	174.461 *** (173.588 – 175.333)	**<0.001**	161.532 *** (160.371 – 162.693)	**<0.001**	85.180 *** (83.414 – 86.946)	**<0.001**	67.811 *** (64.944 – 70.678)	**<0.001**	16.463 *** (14.402 – 18.523)	**<0.001**	21.199 *** (18.432 – 23.966)	**<0.001**	213.640 *** (173.868 – 253.411)	**<0.001**	0.135 (-4.287 – 4.556)	**<0.001**	2.886 *** (2.346 – 3.425)	**<0.001**	4.656 *** (3.869 – 5.442)	**<0.001**
Disease duration (y.)	-0.311 *** (-0.389 – -0.233)	**<0.001**	-0.261 *** (-0.374 – -0.149)	**<0.001**	0.135 (-0.164 – 0.434)	0.135 (-0.164 – 0.434)	0.246 (-0.238 – 0.730)	0.319	1.219 *** (0.773 – 1.666)	**<0.001**	1.065 *** (0.752 – 1.377)	**<0.001**	92.463 *** (81.821 – 103.104)	**<0.001**	77.930 *** (63.345 – 92.514)	**<0.001**	1.090 *** (0.920 – 1.261)	**<0.001**	0.733 *** (0.589 – 0.877)	**<0.001**
Disease duration^2 (y.)	-	-	-	-	-0.025 * (-0.044 – -0.006)	**0.011**	-0.030 * (-0.059 – -0.002)	**0.034**	0.027 * (0.001 – 0.054)	**0.042**			-2.521 *** (-3.175 – -1.866)	**<0.001**	-1.808 *** (-2.647 – -0.969)	**0.001**	-0.030 *** (-0.042 – -0.018)	**<0.001**		
Time to diagnosis (y.)	0.060 (-0.074 – 0.194)	0.378	0.142 (-0.036 – 0.320)	0.116	0.017 (-0.247 – 0.281)	0.900	0.191 (-0.162 – 0.543)	0.288	0.067 (-0.189 – 0.324)	0.607	-0.091 (-0.486 – 0.303)	0.649	0.135 (-4.287 – 4.556)	0.952	-0.603 (-7.453 – 6.247)	0.862	-0.011 (-0.066 – 0.044)		-0.040 (-0.147 – 0.066)	0.459

Note. Coefficient (95% CI), [a] Greater = Worse, PDQ39: Parkinson's Disease Questionnaire, LEDD: Levodopa Equivalent Daily Dose

Table S4: Fixed effects of non-motor symptoms in men and women

	SAS[a]				**MoCA**[b]				**BDI-I**[a]				**MDS-UPDRS I**[a]				**Sniffin' sticks**[b]				**PDQ-39 subscale bodily discomfort**[a]				**RBDSQ**[a]				**PDSS**[b]			
	Men		**Women**		**Men**		**Women**		**Men**		**Women**		**Men**		**Women**		**Men**		**Women**		**Men**		**Women**		**Men**		**Women**		**Men**		**Women**	
Independent variables	B (CI 95%)	p-values	B (CI 95%)	p-values	B (CI 95%)	p-values	B (CI 95%)	p-values	B (CI 95%)	p-values	B (CI 95%)	p-values	B (CI 95%)	p-values	B (CI 95%)	p-values	B (CI 95%)	p-values	B (CI 95%)	p-values	B (CI 95%)	p-values	B (CI 95%)	p-values	B (CI 95%)	p-values	B (CI 95%)	p-values	B (CI 95%)	p-values	B (CI 95%)	p-values
Intercept	13.712 *** (12.944 – 14.481)	**<0.001**	12.816 *** (11.823 – 13.809)	**<0.001**	25.026 *** (24.502 – 25.549)	**<0.001**	25.892 *** (25.305 – 26.478)	**<0.001**	7.922 *** (6.950 – 8.894)	**<0.001**	9.257 *** (8.008 – 10.507)	**<0.001**	7.319 *** (6.550 – 8.087)	**<0.001**	9.451 *** (8.308 – 10.594)	**<0.001**	8.078 *** (7.703 – 8.452)	**<0.001**	9.302 *** (8.728 – 9.875)	**<0.001**	25.386 *** (22.507 – 28.265)	**<0.001**	36.818 *** (32.568 – 41.068)	**<0.001**	3.888 *** (3.492 – 4.284)	**<0.001**	3.728 *** (3.232 – 4.223)	**<0.001**	114.675 *** (111.620 – 117.729)	**<0.001**	105.303 *** (100.949 – 109.657)	**<0.001**
Disease duration (y.)	-0.057 (-0.224 – 0.110)	0.506	0.173 ** (0.060 – 0.285)	**0.003**	-0.035 (-0.163 – 0.094)	0.595	-0.136 *** (-0.210 – -0.061)	**<0.001**	0.033 (-0.177 – 0.243)	0.756	0.331 *** (0.192 – 0.470)	**<0.001**	0.583 *** (0.481 – 0.685)	**<0.001**	0.423 *** (0.294 – 0.551)	**<0.001**	-0.097 *** (-0.135 – -0.060)	**<0.001**	-0.123 *** (-0.181 – -0.066)	**<0.001**	1.277 *** (0.667 – 1.887)	**<0.001**	0.427 * (0.011 – 0.843)	**0.044**	0.129 *** (0.083 – 0.174)	**<0.001**	0.085 ** (0.026 – 0.144)	**0.005**	-1.909 *** (-2.517 – -1.301)	**<0.001**	-0.663 ** (-1.110 – -0.216)	**0.004**
Disease duration^2 (y.)	0.021 *** (0.011 – 0.031)	**<0.001**	-	-	-0.019 *** (-0.027 – -0.011)	**<0.001**	-	-	0.018 ** (0.006 – 0.031)	**0.004**	-	-	-	-	-	-	-	-	-	-	-0.034 * (-0.067 – -0.001)	**0.045**	-	-	-	-	-	-	0.031 * (0.000 – 0.062)	**0.047**	-	-
Time to diagnosis	0.008 (-0.086 – 0.102)	0.865	-0.053 (-0.182 – 0.077)	0.422	0.025 (-0.043 – 0.093)	0.474	-0.074 (-0.162 – 0.015)	0.105	0.081 (-0.023 – 0.185)	0.129	-0.085 (-0.245 – 0.076)	0.300	0.052 (-0.045 – 0.150)	0.292	-0.014 (-0.167 – 0.139)	0.860	-0.009 (-0.055 – 0.038)	0.709	0.034 (-0.038 – 0.107)	0.355	-0.091 (-0.428 – 0.245)	0.594	-0.063 (-0.578 – 0.452)	0.810	0.066 * (0.013 – 0.119)	**0.015**	0.005 (-0.061 – 0.071)	0.878	-0.213 (-0.562 – 0.137)	0.232	0.112 (-0.425 – 0.648)	0.682

Note. [a]Greater = Worse, [b] Greater = Better, Abbreviations: DD = Disease duration, B = disease duration coefficient (95% CI), BDI-I: Beck Depression Inventory, MoCA: Montreal Cognitive Assessment, MDS: Movement Disorders Society, PDQ39: Parkinson's Disease Questionnaire, PDSS: Parkinson's Disease Sleep Scale, RBDSQ: RBD Screening Questionnaire, SAS: Starkstein Apathy Scale, UPDRS: Unified Parkinson's Disease Rating Scale

Table S5: Fixed effects of motor symptoms in men and women

	FMCS[b]				**MDS-UPDRS II**[a]				**MDS-UPDRS III**[a]				**MDS-UPDRS IV**[a]				**MDS-PIGD score**[a]				**MDS-based tremor scale**[a]				**MDT-PD**[a]			
	Men		**Women**		**Men**		**Women**		**Men**		**Women**		**Men**		**Women**		**Men**		**Women**		**Men**		**Women**		**Men**		**Women**	
Independent variables	B (CI 95%)	p-values	B (CI 95%)	p-values	B (CI 95%)	p-values	B (CI 95%)	p-values	B (CI 95%)	p-values	B (CI 95%)	p-values	B (CI 95%)	p-values	B (CI 95%)	p-values	B (CI 95%)	p-values	B (CI 95%)	p-values	B (CI 95%)	p-values	B (CI 95%)	p-values	B (CI 95%)	p-values	B (CI 95%)	p-values
Intercept	88.066 *** (85.682 – 90.450)	**<0.001**	82.423 *** (78.790 – 86.057)	**<0.001**	6.310 *** (5.396 – 7.224)	**<0.001**	6.736 *** (5.569 – 7.904)	**<0.001**	29.689 *** (27.985 – 31.393)	**<0.001**	26.313 *** (24.029 – 28.597)	**<0.001**	0.023 (-0.205 – 0.251)	0.843	-0.144 (-0.654 – 0.365)	0.577	1.780 *** (1.399 – 2.162)	**<0.001**	2.245 *** (1.636 – 2.855)	**<0.001**	0.609 *** (0.556 – 0.662)	**<0.001**	0.503 *** (0.419 – 0.588)	**<0.001**	5.885 *** (4.600 – 7.171)	**<0.001**	6.239 *** (4.300 – 8.178)	**<0.001**
Disease duration (y.)	-2.579 *** (-2.960 – -2.199)	**<0.001**	-1.858 *** (-2.290 – -1.426)	**<0.001**	0.942 *** (0.724 – 1.160)	**<0.001**	0.875 *** (0.726 – 1.023)	**<0.001**	1.273 *** (1.033 – 1.514)	**<0.001**	1.069 *** (0.758 – 1.380)	**<0.001**	0.242 *** (0.196 – 0.287)	**<0.001**	0.524 *** (0.378 – 0.669)	**<0.001**	0.226 *** (0.120 – 0.333)	**<0.001**	0.163 * (0.017 – 0.310)	**0.029**	-0.010 ** (-0.017 – -0.004)	**0.001**	-0.014 (-0.033 – 0.005)	0.141	0.734 *** (0.557 – 0.910)	**<0.001**	0.761 *** (0.514 – 1.008)	**<0.001**
Disease duration ^2 (y.)					0.025 *** (0.013 – 0.038)	**<0.001**									-0.019 *** (-0.028 – -0.011)	**<0.001**	0.020 *** (0.013 – 0.027)	**<0.001**	0.013 ** (0.005 – 0.021)	**0.002**			0.000 (-0.001 – 0.001)	0.858				
Time to diagnosis (y.)	-0.074 (-0.408 – 0.259)	0.662	0.029 (-0.486 – 0.544)	0.911	0.035 (-0.084 – 0.154)	0.561	0.028 (-0.150 – 0.206)	0.756	0.103 (-0.118 – 0.324)	0.359	0.255 (-0.054 – 0.564)	0.105	0.007 (-0.020 – 0.035)	0.601	-0.023 (-0.082 – 0.035)	0.434	-0.008 (-0.056 – 0.041)	0.749	0.035 (-0.047 – 0.116)	0.400	0.002 (-0.005 – 0.008)	0.645	0.017 *** (0.007 – 0.026)	**<0.001**	0.126 (-0.038 – 0.290)	0.133	0.093 (-0.168 – 0.354)	0.485

Note. [a] Greater = Worse, [b] Greater = Better, Abbreviations: DD = Disease duration, B = disease duration coefficient (95% CI), FMCS: Functional Mobility Composite Score, MDS: Movement Disorders Society, MDT: Munich Dysphagia Test, PIGD: Postural Instabilities and Gait Disorders, UPDRS: Unified Parkinson's Disease Rating Scale

3. Supplementary figures

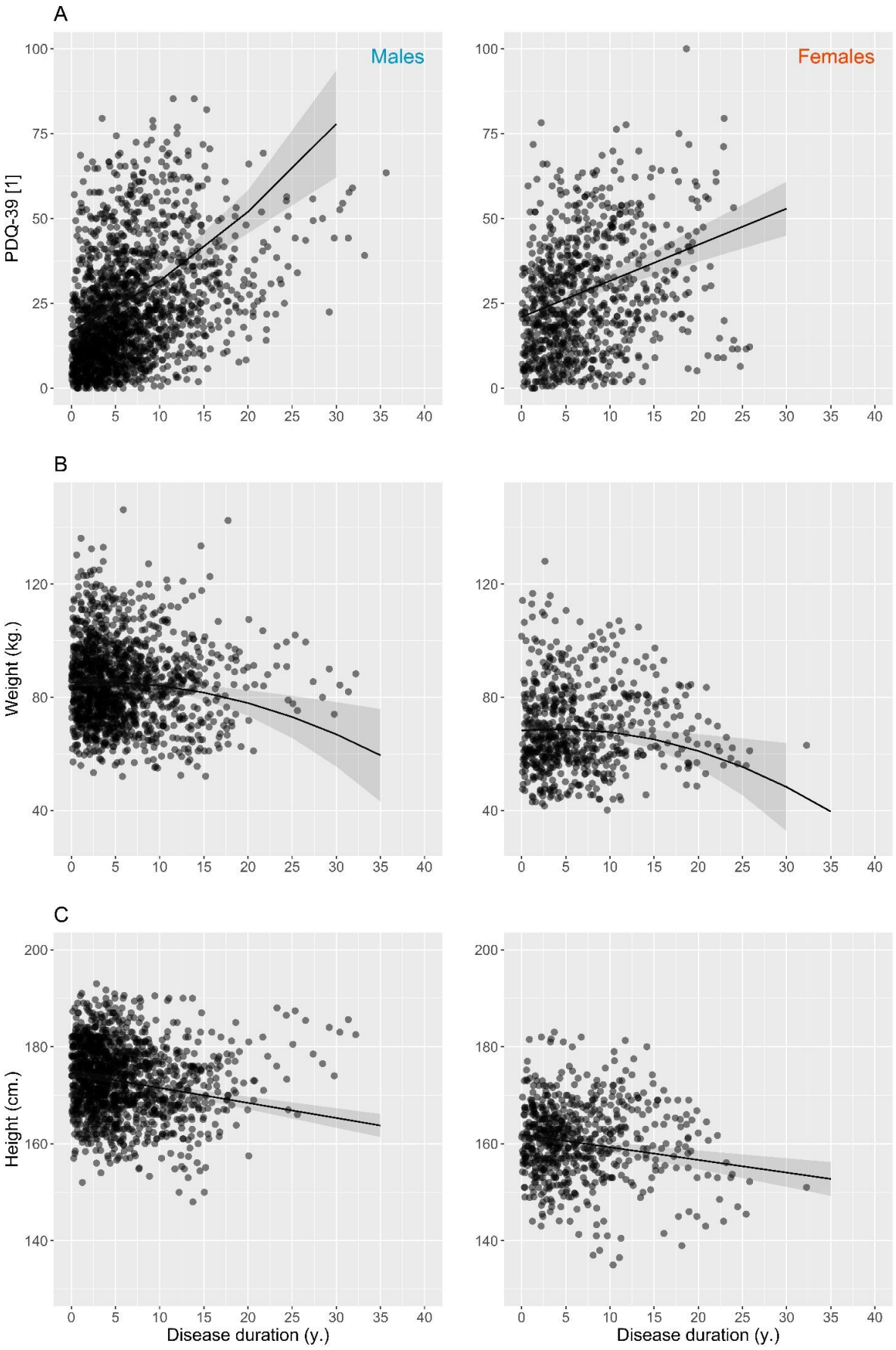

Figure S1: Progression of secondary outcomes, Marginal effect (95% CI), 1 Greater = Worse, 2 Greater = Better

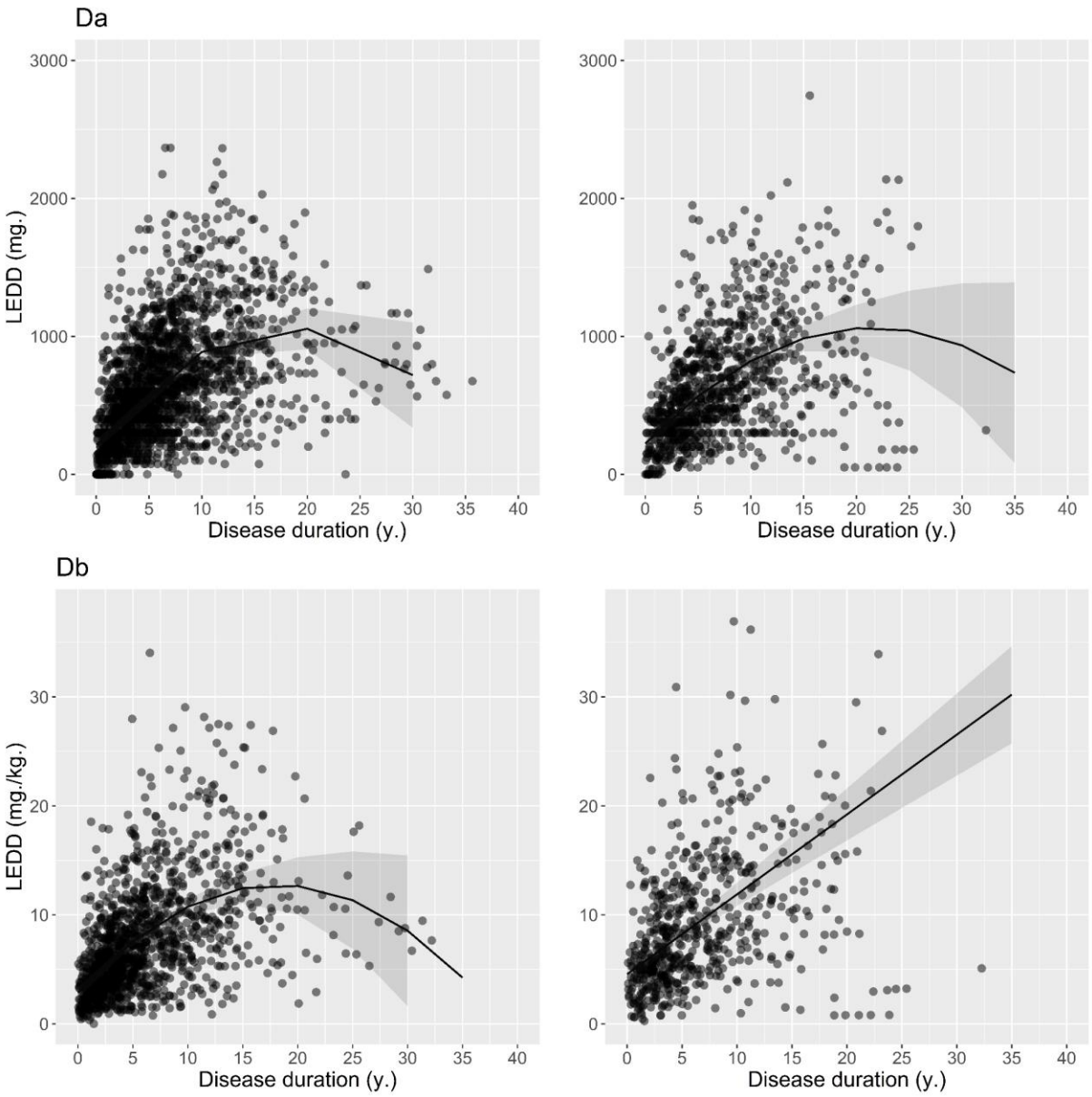

Figure S2: Progression of Levodopa Equivalent Daily Dose (LEDD), Marginal effect (95% CI), 1 Greater = Worse, 2 Greater = Better

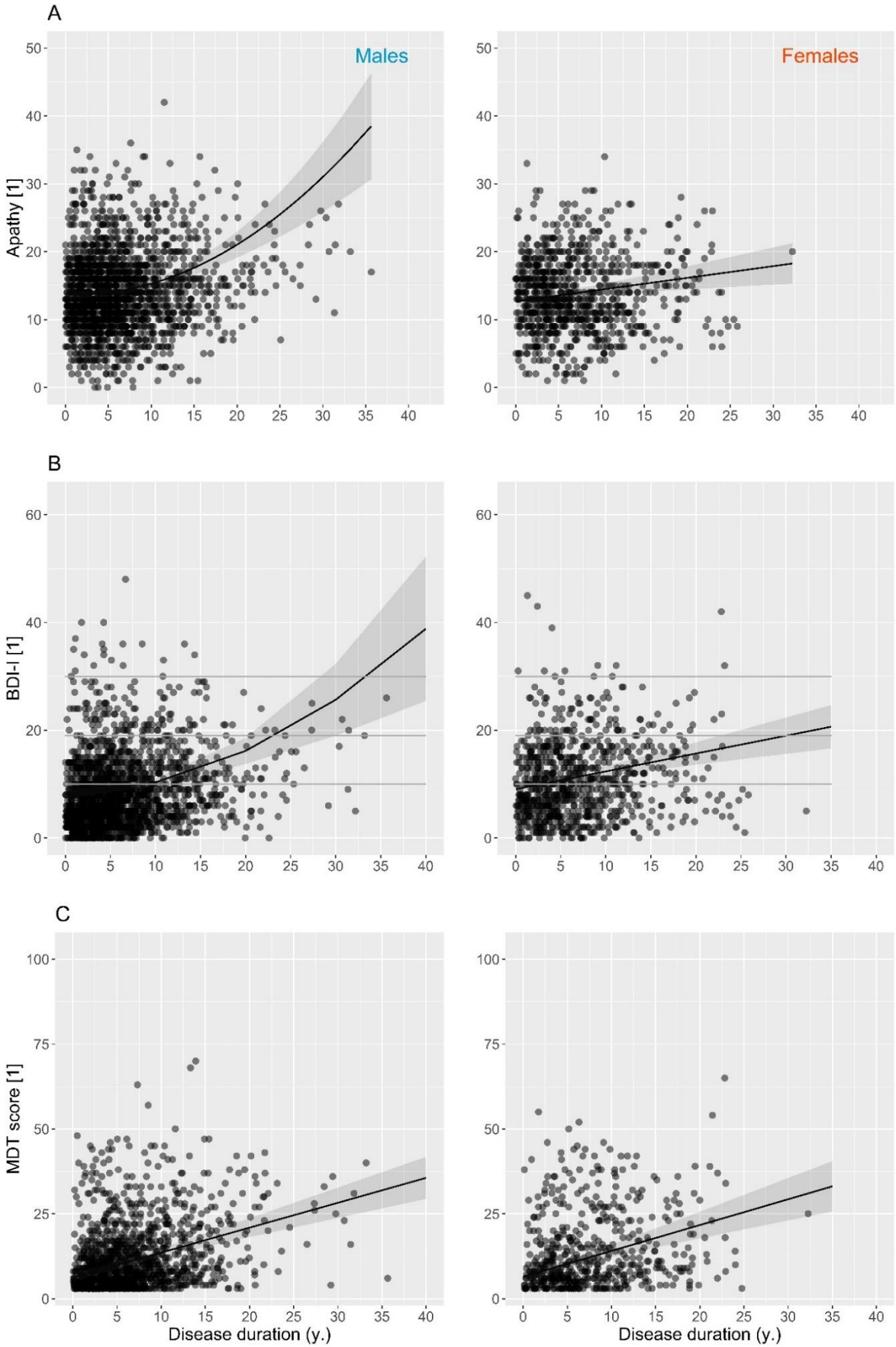

Figure S3: Progression of apathy, depression and dysphagia, Marginal effect (95% CI), 1 Greater = Worse, 2 Greater = Better

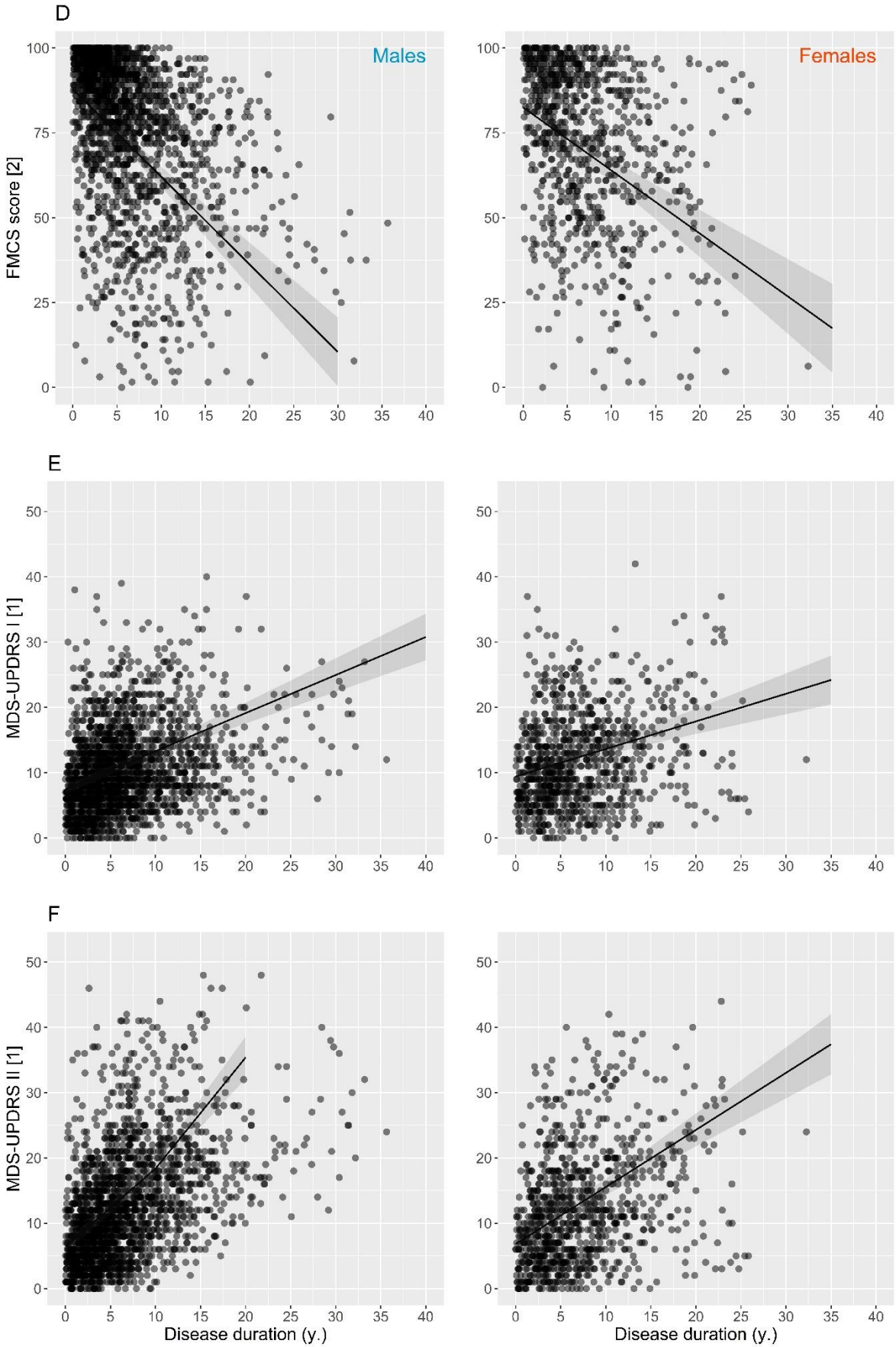

Figure S4: Progression of functional mobility, motor- and non-motor symptoms, Marginal effect (95% CI), 1 Greater = Worse, 2 Greater = Better

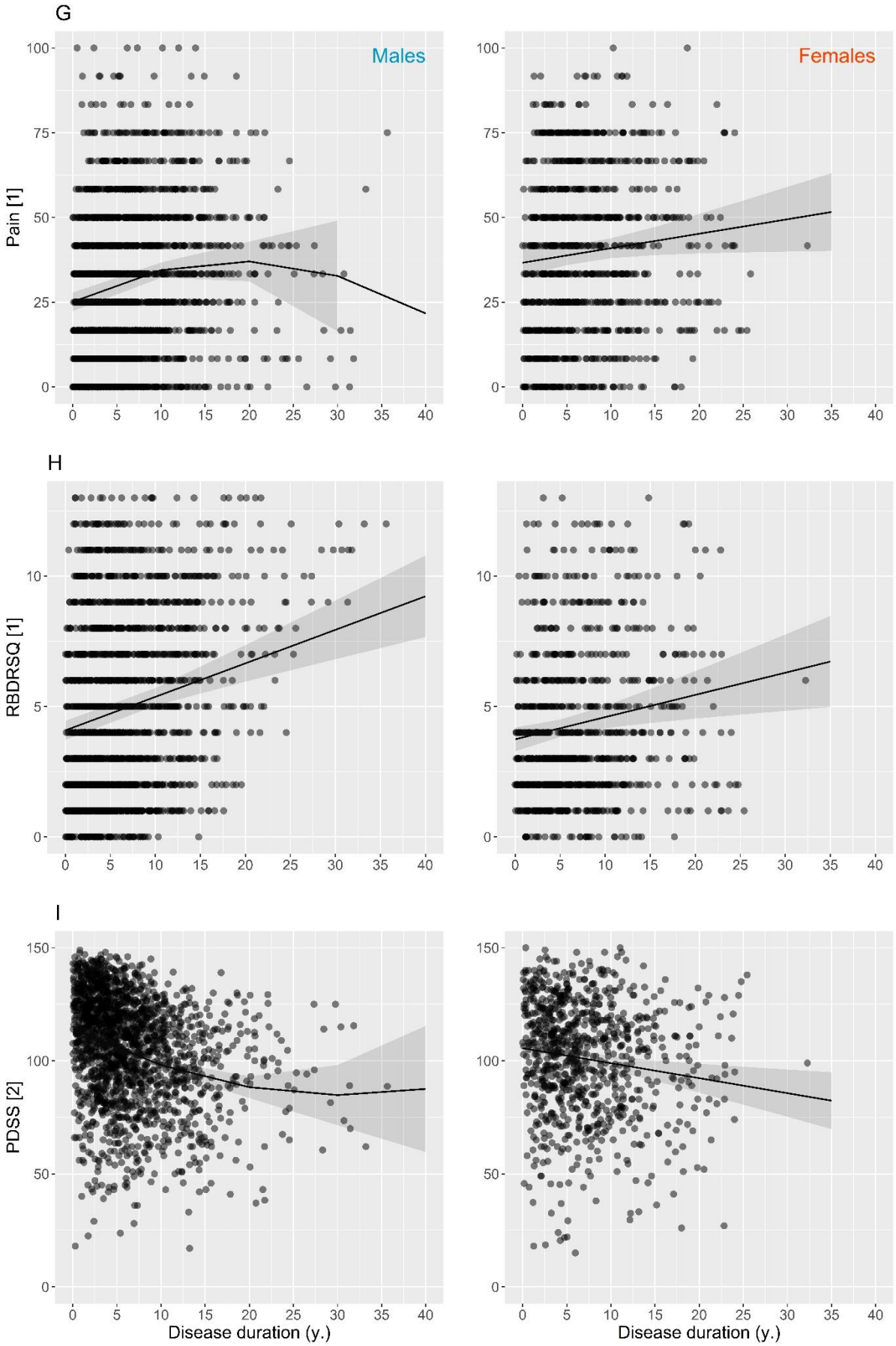

Figure S5: Progression of pain, REM and quality of sleep, Marginal effect (95% CI), 1 Greater = Worse, 2 Greater = Better

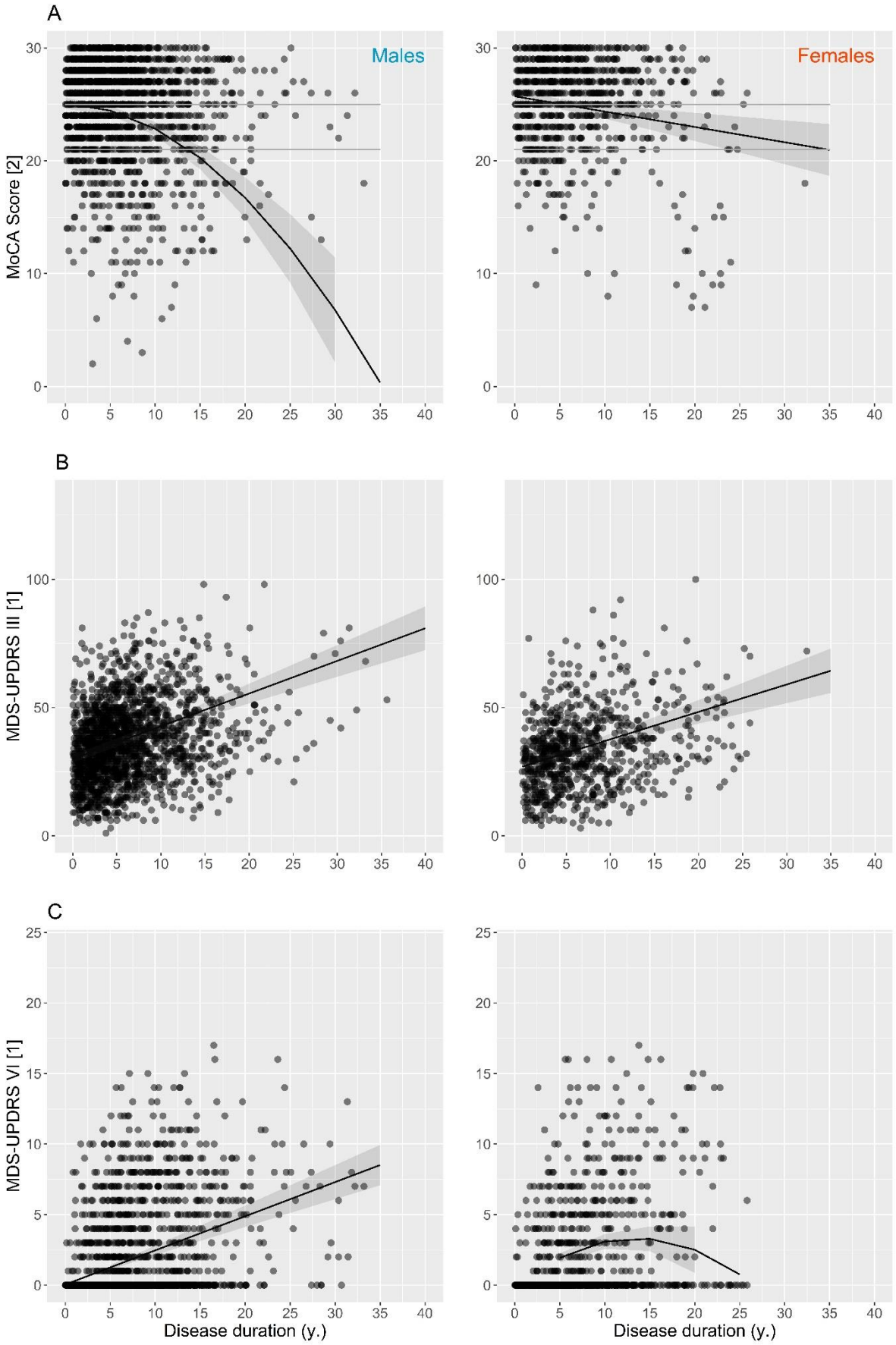

Figure S6: Progression of cognition, MDS-UPDRS III & IV, Marginal effect (95% CI), 1 Greater = Worse, 2 Greater = Better

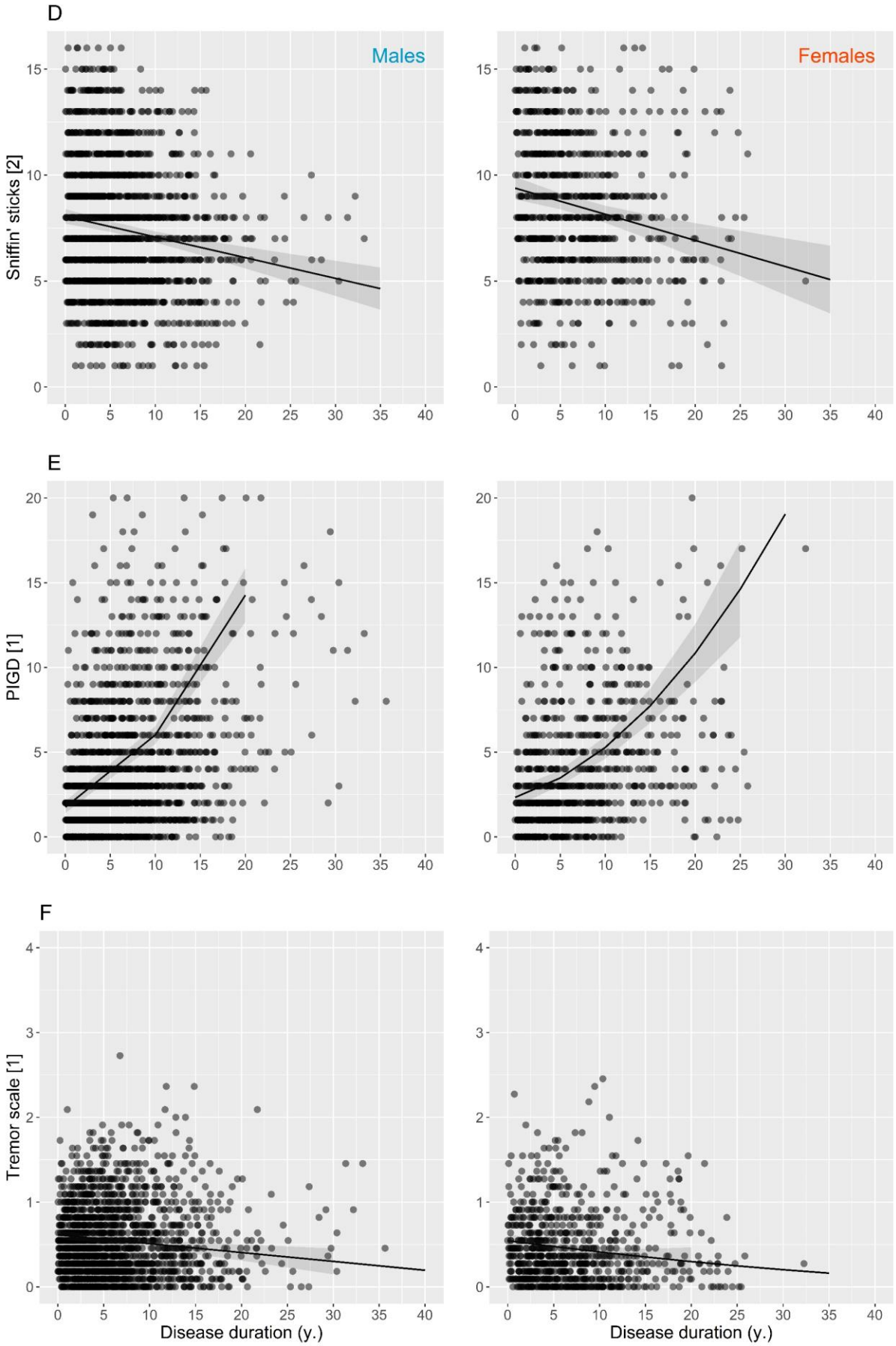

Figure S7: Progression of olfaction, PIGD and tremor, Marginal effect (95% CI), 1 Greater = Worse, 2 Greater = Better

4. STROBE Reporting guideline – cohort studies [7]

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	5
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5-6
Bias	9	Describe any efforts to address potential sources of bias	22
Study size	10	Explain how the study size was arrived at	9
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7-8
		(*b*) Describe any methods used to examine subgroups and interactions	7-8
		(*c*) Explain how missing data were addressed	11
		(*d*) If applicable, explain how loss to follow-up was addressed	
		(*e*) Describe any sensitivity analyses	NA
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9
		(b) Give reasons for non-participation at each stage	9
		(c) Consider use of a flow diagram	9
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	10
		(b) Indicate number of participants with missing data for each variable of interest	33-34
		(c) Summarise follow-up time (eg, average and total amount)	10
Outcome data	15*	Report numbers of outcome events or summary measures over time	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	17-18
		(*b*) Report category boundaries when continuous variables were categorized	NA
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			
Key results	18	Summarise key results with reference to study objectives	19
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	22
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	19-21
Generalisability	21	Discuss the generalisability (external validity) of the study results	22
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	28