

Supplementary Material

Sex-Related Longitudinal Change of Motor, Non-Motor, and Biological Features in Early Parkinson's Disease

Supplementary Table 1. MDS-UPRDS Part I individual items over time in PD patients

Variable	Men (N = 277)						Women (N = 146)						P Interaction (Sex vs Time)**	p Time**	Time Effect **
	Baseline (N = 277)	Month 12 (N = 261)	Month 24 (N = 248)	Month 36 (N = 239)	Month 48 (N = 230)	Month 60 (N = 210)	Baseline (N = 146)	Month 12 (N = 136)	Month 24 (N = 130)	Month 36 (N = 127)	Month 48 (N = 117)	Month 60 (N = 107)			
1.1 Cognitive impairment															
0-1 (ref. group)	267 (96%)	244 (94%)	225 (91%)	214 (90%)	196 (86%)	180 (86%)	143 (98%)	134 (99%)	121 (93%)	118 (93%)	108 (94%)	96 (91%)	0.759	<0.001	1.36
2+	10 (4%)	15 (6%)	23 (9%)	25 (10%)	32 (14%)	29 (14%)	3 (2%)	2 (1%)	9 (7%)	9 (7%)	7 (6%)	10 (9%)			
Missing	0	2	0	0	2	1	0	0	0	0	2	1			
1.2 Hallucinations and psychosis*															
0-1 (ref. group)	277 (100%)	259 (100%)	247 (100%)	236 (99%)	224 (98%)	204 (98%)	146 (100%)	136 (100%)	127 (98%)	125 (98%)	112 (97%)	103 (97%)	0.326	<0.001	1.81
2+	0 (0%)	0 (0%)	1 (0%)	3 (1%)	4 (2%)	5 (2%)	0 (0%)	0 (0%)	3 (2%)	2 (2%)	3 (3%)	3 (3%)			
Missing	0	2	0	0	2	1	0	0	0	0	2	1			
1.3 Depressed mood															
0-1 (ref. group)	267 (96%)	243 (94%)	226 (91%)	221 (92%)	212 (93%)	193 (92%)	141 (97%)	124 (91%)	117 (90%)	114 (90%)	105 (91%)	92 (87%)	0.375	<0.001	1.17
2+	10 (4%)	16 (6%)	22 (9%)	18 (8%)	16 (7%)	16 (8%)	5 (3%)	12 (9%)	13 (10%)	13 (10%)	10 (9%)	14 (13%)			
Missing	0	2	0	0	2	1	0	0	0	0	2	1			
1.4 Anxious mood															
0-1 (ref. group)	263 (95%)	241 (93%)	231 (93%)	224 (94%)	207 (91%)	186 (89%)	139 (95%)	121 (89%)	119 (92%)	110 (87%)	102 (89%)	89 (84%)	0.608	<0.001	1.20
2+	14 (5%)	18 (7%)	17 (7%)	15 (6%)	21 (9%)	23 (11%)	7 (5%)	15 (11%)	11 (8%)	17 (13%)	13 (11%)	17 (16%)			
Missing	0	2	0	0	2	1	0	0	0	0	2	1			
1.5 Apathy															
0-1 (ref. group)	271 (98%)	243 (94%)	224 (90%)	224 (94%)	206 (90%)	180 (86%)	141 (97%)	123 (90%)	119 (92%)	114 (90%)	103 (90%)	97 (92%)	0.060	<0.001	1.25
2+	6 (2%)	16 (6%)	24 (10%)	15 (6%)	22 (10%)	29 (14%)	5 (3%)	13 (10%)	11 (8%)	13 (10%)	12 (10%)	9 (8%)			
Missing	0	2	0	0	2	1	0	0	0	0	2	1			
1.6 Features of dopamine dysregulation syndrome**															
0-1 (ref. group)	276 (100%)	258 (100%)	246 (99%)	235 (98%)	223 (98%)	203 (97%)	146 (100%)	135 (99%)	127 (98%)	125 (98%)	114 (99%)	101 (95%)	0.891	<0.001	1.57
2+	1 (0%)	1 (0%)	2 (1%)	4 (2%)	5 (2%)	6 (3%)	0 (0%)	1 (1%)	3 (2%)	2 (2%)	1 (1%)	5 (5%)			
Missing	0	2	0	0	2	1	0	0	0	0	2	1			
1.7 Sleep problems															
0-1 (ref. group)	214 (77%)	182 (70%)	173 (70%)	157 (66%)	132 (58%)	122 (58%)	109 (75%)	90 (66%)	80 (62%)	79 (62%)	66 (56%)	53 (50%)	0.806	<0.001	1.22

2+	63 (23%)	77 (30%)	75 (30%)	82 (34%)	96 (42%)	87 (42%)	36 (25%)	46 (34%)	50 (38%)	48 (38%)	51 (44%)	53 (50%)			
Missing	0	2	0	0	2	1	1	0	0	0	0	1			
1.8 Daytime sleepiness															
0-1 (ref. group)	216 (78%)	182 (70%)	161 (65%)	135 (56%)	116 (51%)	104 (50%)	120 (83%)	105 (77%)	91 (70%)	82 (65%)	74 (63%)	65 (61%)			
2+	61 (22%)	77 (30%)	87 (35%)	104 (44%)	112 (49%)	105 (50%)	25 (17%)	31 (23%)	39 (30%)	45 (35%)	43 (37%)	41 (39%)	0.604	<0.001	1.29
Missing	0	2	0	0	2	1	1	0	0	0	0	1			
1.9 Pain and others															
0-1 (ref. group)	246 (89%)	214 (83%)	209 (84%)	198 (83%)	168 (74%)	163 (78%)	123 (85%)	108 (79%)	106 (82%)	93 (73%)	91 (78%)	77 (73%)			
2+	31 (11%)	45 (17%)	39 (16%)	41 (17%)	60 (26%)	46 (22%)	22 (15%)	28 (21%)	24 (18%)	34 (27%)	26 (22%)	29 (27%)	0.680	<0.001	1.17
Missing	0	2	0	0	2	1	1	0	0	0	0	1			
1.10 Urinary															
0-1 (ref. group)	247 (89%)	221 (85%)	195 (79%)	176 (74%)	161 (71%)	142 (68%)	125 (86%)	113 (83%)	109 (84%)	105 (83%)	92 (79%)	82 (77%)			
2+	30 (11%)	38 (15%)	53 (21%)	63 (26%)	67 (29%)	67 (32%)	20 (14%)	23 (17%)	21 (16%)	22 (17%)	25 (21%)	24 (23%)	0.023	M: <0.001 W: 0.033	M: 1.33 W: 1.13
Missing	0	2	0	0	2	1	1	0	0	0	0	1			
1.11 Constipation															
0-1 (ref. group)	258 (93%)	235 (91%)	217 (88%)	205 (86%)	196 (86%)	170 (81%)	133 (92%)	114 (84%)	107 (82%)	109 (86%)	97 (83%)	85 (80%)			
2+	19 (7%)	24 (9%)	31 (13%)	34 (14%)	32 (14%)	39 (19%)	12 (8%)	22 (16%)	23 (18%)	18 (14%)	20 (17%)	21 (20%)	0.381	<0.001	1.21
Missing	0	2	0	0	2	1	1	0	0	0	0	1			
1.12 Lightheadedness															
0-1 (ref. group)	269 (97%)	244 (94%)	225 (91%)	212 (89%)	195 (86%)	170 (81%)	138 (95%)	131 (96%)	120 (92%)	117 (92%)	110 (94%)	95 (90%)			
2+	8 (3%)	15 (6%)	23 (9%)	27 (11%)	33 (14%)	39 (19%)	7 (5%)	5 (4%)	10 (8%)	10 (8%)	7 (6%)	11 (10%)	0.041	M: <.001 W: 0.028	M: 1.47 W: 1.20
Missing	0	2	0	0	2	1	1	0	0	0	0	1			
1.13 Fatigue															
0-1 (ref. group)	251 (91%)	218 (84%)	194 (78%)	187 (78%)	165 (72%)	138 (66%)	124 (86%)	111 (82%)	107 (82%)	106 (83%)	97 (83%)	77 (73%)			
2+	26 (9%)	41 (16%)	54 (22%)	52 (22%)	63 (28%)	71 (34%)	21 (14%)	25 (18%)	23 (18%)	21 (17%)	20 (17%)	29 (27%)	0.011	M: <0.001 W: 0.007	M: 1.34 W: 1.15
Missing	0	2	0	0	2	1	1	0	0	0	0	1			

Note: All models are also adjusted for Baseline BMI, Vascular Risk Factor Score (VRF) and Side Most Affected.

* Models are adjusted for Baseline BMI and VRF only.

**If interaction is significant, we find time effect p-value for each men and women separately. Otherwise, we provide time effect p-value without stratifying by gender.

Significance level for comparisons is $p < 0.004$ (after Bonferroni correction).

MDS-UPDRS: Movement Disorders Society Parkinson's Disease Rating Scale

Supplementary Table 2. Cognitive performance over time in healthy controls

Variable	Enrolled Subjects												p Interaction (Sex vs Time) **	p Time **	Time Effect **
	Men (N = 126)						Women (N = 70)								
	Baseline (N = 126)	Month 12 (N = 118)	Month 24 (N = 108)	Month 36 (N = 103)	Month 48 (N = 100)	Month 60 (N = 96)	Baseline (N = 70)	Month 12 (N = 67)	Month 24 (N = 66)	Month 36 (N = 64)	Month 48 (N = 62)	Month 60 (N = 60)			
MoCA															
Mean (SD)	28.2 (1.1)	27.1 (2.2)	26.9 (2.5)	27.3 (2.2)	27.5 (2.3)	27.3 (2.2)	28.3 (1.1)	27.5 (2.1)	27.9 (2.0)	27.8 (2.1)	27.8 (2.4)	28.0 (2.1)	0.074	<0.001	-0.11
Min.-Max.	26.0-30.0	20.0-30.0	21.0-30.0	19.0-30.0	20.0-30.0	20.0-30.0	27.0-30.0	21.0-30.0	22.0-30.0	23.0-30.0	19.0-30.0	21.0-30.0			
Missing	0	0	1	0	1	0	0	0	0	0	0	2			
HVLT immediate recall															
Mean (SD)	25.4 (4.4)	25.7 (4.7)	24.9 (4.8)	25.6 (5.4)	25.4 (5.3)	25.9 (5.9)	27.3 (4.4)	27.5 (4.5)	27.4 (5.1)	28.0 (4.8)	27.5 (4.4)	29.4 (3.8)	0.039	M: 0.690 W: 0.002	M: 0.04 W: 0.33
Min.-Max.	15.0-34.0	13.0-35.0	12.0-36.0	11.0-36.0	12.0-36.0	10.0-36.0	16.0-35.0	17.0-36.0	11.0-35.0	14.0-35.0	18.0-34.0	21.0-35.0			
Missing	0	0	0	0	2	0	0	0	0	0	0	2			
HVLT delayed recall															
Mean (SD)	9.0 (2.5)	8.8 (2.6)	8.8 (2.5)	8.9 (2.7)	8.7 (2.5)	9.2 (2.9)	9.9 (1.9)	9.7 (2.2)	10.0 (2.4)	9.7 (2.2)	9.9 (2.2)	10.4 (2.2)	0.217	0.096	0.05
Min.-Max.	2.0-12.0	0.0-12.0	1.0-12.0	0.0-12.0	2.0-12.0	0.0-12.0	4.0-12.0	3.0-12.0	0.0-12.0	3.0-12.0	0.0-12.0	0.0-12.0			
Missing	0	0	0	0	2	0	0	0	0	0	0	2			
Benton Judgement of Line Orientation															
Mean (SD)	13.5 (1.8)	13.2 (2.2)	13.5 (1.8)	13.1 (2.0)	13.2 (2.2)	13.2 (1.9)	12.4 (2.2)	11.6 (2.6)	12.4 (2.4)	11.7 (2.4)	12.4 (2.7)	12.0 (2.6)	0.923	0.042	-0.06
Min.-Max.	8.0-15.0	5.0-15.0	6.0-15.0	7.0-15.0	0.0-15.0	6.0-15.0	4.0-15.0	4.0-15.0	2.0-15.0	6.0-15.0	4.0-15.0	6.0-15.0			
Missing	0	0	0	0	2	0	0	0	0	0	1	2			
Symbol Digit Modalities Test															
Mean (SD)	45.6 (10.6)	46.2 (11.4)	45.4 (10.9)	46.8 (11.7)	45.1 (11.6)	46.0 (12.2)	48.8 (10.1)	49.8 (10.0)	48.2 (10.1)	49.8 (9.6)	48.9 (10.0)	50.3 (10.2)	0.657	0.420	0.11
Min.-Max.	20.0-83.0	21.0-83.0	26.0-80.0	21.0-91.0	24.0-88.0	21.0-81.0	27.0-71.0	28.0-76.0	25.0-73.0	30.0-75.0	29.0-74.0	32.0-83.0			
Missing	0	0	0	0	2	0	0	0	0	1	0	2			
Letter Number Sequencing															
Mean (SD)	10.8 (2.7)	11.0 (2.5)	10.8 (2.5)	11.0 (2.7)	10.8 (2.8)	10.7 (2.8)	11.0 (2.3)	10.8 (2.9)	11.1 (2.6)	11.1 (2.9)	11.1 (2.7)	11.6 (2.9)	0.045	M: 0.218 W: 0.112	M: - 0.06 W: 0.08
Min.-Max.	2.0-20.0	6.0-19.0	5.0-19.0	5.0-20.0	3.0-17.0	4.0-20.0	7.0-19.0	5.0-19.0	6.0-18.0	5.0-20.0	5.0-20.0	5.0-20.0			
Missing	0	0	0	0	2	0	0	0	0	0	0	2			
Semantic Fluency															
Mean (SD)	49.0 (10.5)	49.9 (11.2)	50.1 (11.0)	50.1 (11.8)	49.5 (11.9)	49.8 (12.1)	56.8 (10.7)	57.0 (9.7)	56.8 (11.5)	57.2 (10.8)	55.7 (10.5)	58.0 (11.4)	0.484	0.394	0.12
Min.-Max.	22.0-80.0	25.0-86.0	20.0-83.0	23.0-88.0	18.0-85.0	23.0-87.0	33.0-75.0	31.0-79.0	26.0-79.0	32.0-77.0	31.0-75.0	36.0-83.0			
Missing	0	0	0	0	2	0	0	0	0	0	0	2			

Note: All models are also adjusted for Baseline BMI and Vascular Risk Factor Score (VRF).

Significance level for comparisons is p<0.007 (after Bonferroni correction).

**If interaction is significant, we find time effect p-value for each men and women separately. Otherwise, we provide time effect p-value without stratifying by sex.

MoCA, Montreal Cognitive Assessment; HVLT, Hopkins Verbal Learning Test; M, men; W, women

Supplementary Table 3. Participant's time to experiencing event

Variable	Men						Women						Hazard Ratio	p
	BL	Month 12	Month 24	Month 36	Month 48	Month 60	BL	Month 12	Month 24	Month 36	Month 48	Month 60		
Initiation of Symptomatic Therapy: LED >0 N Subjects Remaining N (%) with event since previous visit	277 0 (0%)	261 153 (58.6%)	102 60 (58.8%)	46 21 (45.7%)	26 7 (26.9%)	18 3 (16.7%)	146 0 (0%)	136 72 (52.9%)	65 33 (50.8%)	32 12 (37.5%)	19 3 (15.8%)	17 0 (0%)	1.273	0.037
Initiation of Surgical Treatment (DBS or LCIG) N Subjects Remaining N (%) with event since previous visit	277 0 (0%)	261 0 (0%)	248 0 (0%)	239 1 (0.4%)	229 2 (0.9%)	207 2 (1%)	146 0 (0%)	136 0 (0%)	130 0 (0%)	127 0 (0%)	117 1 (0.9%)	106 4 (3.8%)	0.603	0.442
Motor Fluctuations: MDS UPDRS part IV >0 N Subjects Remaining N (%) with event since previous visit	277 0 (0%)	259 14 (5.4%)	235 29 (12.3%)	202 26 (12.9%)	167 33 (19.8%)	125 41 (32.8%)	146 0 (0%)	136 13 (9.6%)	117 14 (12%)	100 17 (17%)	77 12 (15.6%)	57 13 (22.8%)	0.977	0.881
Dyskinesia: MDS-UPDRS 4.1 and 4.2 N Subjects Remaining N (%) with event since previous visit	277 0 (0%)	261 2 (0.8%)	246 8 (3.3%)	230 8 (3.5%)	214 14 (6.5%)	182 24 (13.2%)	146 0 (0%)	136 2 (1.5%)	128 7 (5.5%)	118 8 (6.8%)	102 7 (6.9%)	86 12 (14%)	0.843	0.450
Motor Fluctuation: MDS-UPDRS 4.3, 4.4 and 4.5 N Subjects Remaining N (%) with event since previous visit	277 0 (0%)	261 11 (4.2%)	238 25 (10.5%)	209 22 (10.5%)	179 33 (18.4%)	134 44 (32.8%)	146 0 (0%)	136 9 (6.6%)	121 12 (9.9%)	106 16 (15.1%)	84 13 (15.5%)	64 11 (17.2%)	1.034	0.839

Significance level for comparisons is $p < 0.010$ (after Bonferroni correction).

Supplementary Table 4. Utilization of medication classes over time in PD

Variable	Men (N = 126)						Women (N = 70)						P Interaction (Sex vs Time)	p Time	Time Effect **
	Baseline (N = 277)	Month 12 (N = 261)	Month 24 (N = 248)	Month 36 (N = 239)	Month 48 (N = 230)	Month 60 (N = 210)	Baseline (N = 146)	Month 12 (N = 136)	Month 24 (N = 130)	Month 36 (N = 127)	Month 48 (N = 117)	Month 60 (N = 107)			
Medications for Cognition	0 (0%)	2 (1%)	4 (2%)	8 (3%)	12 (5%)	14 (7%)	0 (0%)	0 (0%)	1 (1%)	2 (2%)	4 (3%)	2 (2%)	0.847	<0.001	1.75
Anti-depressants	39 (14%)	44 (17%)	53 (21%)	54 (23%)	57 (25%)	48 (23%)	38 (26%)	40 (29%)	41 (32%)	41 (32%)	41 (35%)	36 (34%)	0.728	<0.001	1.11
Anxiolytics*	18 (6%)	15 (6%)	19 (8%)	18 (8%)	21 (9%)	18 (9%)	15 (10%)	15 (11%)	16 (12%)	10 (8%)	10 (9%)	9 (8%)	0.206	0.593	1.02
Antipsychotics*	0 (0%)	0 (0%)	2 (1%)	6 (3%)	4 (2%)	2 (1%)	0 (0%)	0 (0%)	0 (0%)	2 (2%)	3 (3%)	5 (5%)	0.056	<0.001	1.87
Missing	0	0	0	0	0	0	0	0	0	0	0	0			

Note: All models are also adjusted for Baseline BMI, Vascular Risk Factor Score and side most affected.

* Models are adjusted for Baseline BMI and VRF only.

**If interaction is significant, we find time effect p-value for each men and women separately. Otherwise, we provide time effect p-value without stratifying by gender.

Significance level for comparisons is $p < 0.013$ (after Bonferroni correction).

Supplementary Table 5. DaTScan SBR* over time

Variable	Men				Women				p Interaction (Sex vs Time)**	p Time	Time Effect
	Baseline (N = 277)	Month 12 (N = 261)	Month 24 (N = 248)	Month 48 (N = 230)	Baseline (N = 146)	Month 12 (N = 136)	Month 24 (N = 130)	Month 48 (N = 117)			
Contralateral Caudate											
Mean (SD)	1.825 (0.552)	1.625 (0.494)	1.527 (0.523)	1.314 (0.510)	1.861 (0.570)	1.653 (0.504)	1.526 (0.515)	1.405 (0.478)	0.581	<0.001	-0.12
Ipsilateral Caudate											
Mean (SD)	2.114 (0.591)	1.884 (0.537)	1.793 (0.573)	1.551 (0.572)	2.230 (0.597)	2.010 (0.558)	1.857 (0.578)	1.728 (0.518)	0.884	<0.001	-0.13
Contralateral Putamen											
Mean (SD)	0.697 (0.267)	0.606 (0.228)	0.567 (0.227)	0.486 (0.198)	0.685 (0.276)	0.591 (0.249)	0.560 (0.208)	0.517 (0.214)	0.283	<0.001	-0.05
Ipsilateral Putamen											
Mean (SD)	0.943 (0.381)	0.772 (0.304)	0.735 (0.323)	0.582 (0.252)	0.996 (0.383)	0.813 (0.343)	0.748 (0.313)	0.649 (0.247)	0.516	<0.001	-0.09
Mean Striatum											
Mean (SD)	1.395 (0.397)	1.222 (0.344)	1.155 (0.374)	0.983 (0.351)	1.443 (0.407)	1.267 (0.374)	1.173 (0.368)	1.075 (0.327)	0.808	<0.001	-0.10

*DaTscan not collected at year 3.

Significance level for comparisons is $p < 0.010$ (after Bonferroni correction).

**If interaction is significant, we find time effect p-value for men and women separately. Otherwise, we provide time effect p-value without stratifying by sex.

Note: All models are also adjusted for Baseline BMI, Vascular Risk Factor Score (VRF), and Side Most Affected.

Supplementary Table 6. CSF Biologics over time

Variable	Men				Women				p Interaction (Sex vs Time) **	p Time	Time Effect
	Baseline (N = 277)	Month 12 (N = 261)	Month 24 (N = 248)	Month 36 (N = 239)	Baseline (N = 146)	Month 12 (N = 136)	Month 24 (N = 130)	Month 36 (N = 127)			
Alpha-Synuclein											
Mean (SD)	1,459.36	1,406.29	1,393.05	1,426.33	1,595.46	1,464.02	1,535.48	1,446.73	0.084	<0.001	-29.92
Min.-Max.	(647.52)	(616.39)	(580.24)	(548.56)	(694.56)	(626.21)	(691.62)	582.40-			
Missing	432.40- 5,256.90 7	420.00- 3,685.30 43	336.10- 3,593.00 46	442.90- 3,434.70 87	558.10- 4,223.30 2	427.80- 3,298.70 27	625.80- 3,871.40 24	3,621.10 49			
A-Beta											
Mean (SD)	890.39	870.48	879.01	879.40	946.51	930.14	919.23	891.93	0.976	<0.001	-31.35
Min.-Max.	(374.57)	(396.92)	(392.88)	(364.21)	(472.00)	(400.39)	(407.51)	(353.60)			
Missing	249.00- 2,572.00 7	249.50- 2,480.00 44	269.50- 3,000.00 49	240.80- 2,396.00 90	238.80- 3,707.00 6	249.60- 2,149.00 27	260.30- 2,674.00 25	351.80- 1,907.00 54			
T-Tau											
Mean (SD)	166.73	165.15	167.23	169.45	174.77	172.92	173.57 (66.78)	173.74 (64.53)	0.989	<0.001	-27.20
Min.-Max.	(52.19)	(57.90)	(59.65)	(57.16)	(64.36)	(60.08)	88.55-463.60	83.03-444.50			
Missing	80.93-345.30 15	82.24-388.70 47	80.88-367.90 48	80.98-376.50 90	85.00-467.00 5	82.46-359.10 28	24	50			
P-Tau											
Mean (SD)	14.67 (4.86)	14.73 (5.06)	14.87 (5.32)	14.65 (5.11)	15.24 (5.90)	15.03 (5.67)	15.02 (6.28)	15.21 (6.13)	0.680	<0.001	-26.32
Min.-Max.	8.03-31.64	8.09-31.93	8.17-33.19	8.03-33.37	8.01-40.13	8.05-34.28	8.13-43.69	8.32-42.87			
Missing	31	71	69	99	13	34	29	56			
T-Tau/A-Beta											
Mean (SD)	0.20 (0.09)	0.21 (0.10)	0.21 (0.11)	0.21 (0.10)	0.21 (0.11)	0.21 (0.12)	0.21 (0.12)	0.22 (0.14)	0.616	<0.001	-26.26
Min.-Max.	0.10-0.72	0.11-0.76	0.11-0.86	0.11-0.90	0.10-0.84	0.10-0.87	0.10-0.74	0.12-0.92			
Missing	16	49	51	93	9	29	25	55			
P-Tau/A-Beta											
Mean (SD)	0.02 (0.01)	0.02 (0.01)	0.02 (0.01)	0.02 (0.01)	0.02 (0.01)	0.02 (0.01)	0.02 (0.01)	0.02 (0.01)	0.647	<0.001	-25.27
Min.-Max.	0.01-0.07	0.01-0.08	0.01-0.08	0.01-0.08	0.01-0.08	0.01-0.09	0.01-0.08	0.01-0.08			
Missing	32	73	72	102	17	35	30	61			
P-Tau/T-Tau											
Mean (SD)	0.09 (0.01)	0.08 (0.01)	0.08 (0.01)	0.08 (0.01)	0.08 (0.01)	0.08 (0.01)	0.08 (0.01)	0.08 (0.01)	0.606	<0.001	-25.81
Min.-Max.	0.07-0.11	0.06-0.11	0.07-0.10	0.07-0.11	0.07-0.13	0.07-0.11	0.07-0.13	0.07-0.10			
Missing	31	71	69	99	13	34	29	56			

**If interaction is significant, we find time effect p-value for men and women separately. Otherwise, we provide time effect p-value without stratifying by sex. Significance level for comparisons is p<0.0071 (after Bonferroni correction).

Note: All models are also adjusted for Baseline BMI, Vascular Risk Factor Score (VRF) and Side Most Affected. Analyses are based on Rank Based models.

Supplementary Table 7. Other studies evaluating sex differences in PD

Citation	Year	Cohort and design	Sample size	Primary Outcome	Conclusion
Haaxma et al. [1]	2007	Nijmegen Cohort; Disease duration: 2.6 Design: cross-sectional	253: 156 men 97 women	Unified Parkinson's disease rating scale part III; SPECT imaging	The development of symptomatic PD may be delayed by higher physiological striatal dopamine levels, possibly due to the activity of estrogens Women also presented more often with tremor These findings suggest a more benign phenotype in women with PD.
Hassin-Baer et al. [2]	2011	Chaim Sheba Cohort (Israel) Design: longitudinal	155: 90 men 65 women	Appearance of levodopa-induced dyskinesia	Female gender is associated with a significantly shorter latency to levodopa-induced dyskinesia appearance.
Martinez-Martin et al. [3]	2012	International multi-site study Design: cross-sectional	951: 595 men; 355 women	Non-motor symptoms scale (NMSS)	Women reported more fatigue, restless legs, nervousness, sadness, constipation, and pain; men reported more daytime sleepiness, drooling, and sexual complaints
*Solla et al. [4]	2012	Sardinian PD Cohort; mean disease duration 6.3 years Design: cross-sectional	156: 91 men; 65 women	Multiple outcomes (motor and non-motor)	More women had tremor as initial symptom; women had higher postural instability on UPDRS part III, more frequent depression and anxiety. On NMSS, women had more severe symptoms in cardiovascular, sleep/fatigue, and mood/apathy domains and men had higher sexual dysfunction domain scores
Picillo et al. [5]	2014	Naples Italy PD Cohort; early, de novo Design: longitudinal over 2 years	134: 86 men; 48 women	Non-Motor Symptoms Questionnaire (NMSQuest)	Men had more non-motor symptoms compared to women; Men had increased complaints related to urinary urgency, sex drive, daytime sleepiness, weight change; Both men and women had reduction in sadness/blues at follow up.
Lubomski et al. [6]	2014	Victoria Cohort (Australia) Disease duration: 7.3 (5.7) Design: cross-sectional	210: 129 men 81 women	The 39-item Parkinson's disease Questionnaire Summary Index	The disease had a greater overall impact on the health and well-being of male patients
Song et al. [7]	2014	Chinese Parkinson Study Group multicenter Design: cross-sectional	458: 258 men; 170 women	UPDRS and various non-motor symptoms questionnaires	No sex-related difference in total UPDRS scores; women had more depression and lower MMSE scores than men
Augustine et al. [8]	2015	NET-PD (early, treated PD; mean disease duration: 1.5 years Design: cross-sectional	1,741: 1,123 men; 618 women	Multiple Outcomes (motor, non-motor, cognitive, and daily function)	No difference between men and women in motor symptoms or examination; women had better SCOPA-COG and better symbol digit modalities test performance
Colombo et al. [9]	2015	The DEEP study (Italy) Disease duration < 5 years (30%) Design: cross-sectional	617: 381 men 236 women	Wearing Off Questionnaire	Both motor and non-motor wearing off is more common in women
Dahodwala et al. [10]	2016	NPF-POP Design: longitudinal	4679 2938 men; 1741 women	NMSS	There were few sex differences in longitudinal progression except that women had improvement in delayed recall compared to men
Cereda et al. [11]	2016	Parkinson Institute-Milan Italy Design: cross-sectional; retrospective	6599 3848 men; 2751 women	Dementia diagnosis by DSM-IV criteria	Male PD patients had higher rates of dementia

Nicolleti et al. [12]	2017	FRAGAMP multicenter study Design: case control, cross-sectional	585 348 men; 237 women 481 controls	Face to face evaluation of NMS	Compared to PD men, PD women had more depression and urinary symptoms; when controlling for differences compared to controls, men had more cognitive impairment and depression than women
Cholerton et al. [13]	2018	Pacific Udall Center Clinical Consortium Design: longitudinal	418	Progression from normal cognition to MCI or from MCI to dementia	Men progressed more rapidly to cognitive impairment
*Hu et al. [14]	2018	West China Hospital of Sichuan University, early, de novo Design: cross-sectional	569 275 men; 294 women	Non-motor symptoms scale (NMSS), Chinese version	Men had higher UPDRS part III; higher Hoehn and Yahr; higher MoCA; lower depression score and lower anxiety score than women; men had more sexual and urinary complaints and women had more sleep/fatigue; mood/apathy; and attention/memory complaints.
Iwaki et al. [15]	2021	Twelve longitudinal PD cohorts	5946	Multiple outcomes	Women were less likely to develop cognitive impairment over time, more likely to develop dyskinesia, had less progression of UPDRS part II scores (driven by non-de-novo cohorts), and less progression of total UPDRS; as well as lower baseline UPDRS part III compared to men
Bakeberg et al. [16]	2021	Australian Parkinson's Disease Registry; disease duration: 7.9 (5.7) Design: cross-sectional and longitudinal	Cross-sectional: 392: 253 men; 139 women Longitudinal: 197 80 men; 47 women	Addenbrooke's Cognitive Examination	Women had better cross-sectional global cognitive performance and men had higher LED and more men had undergone DBS Men had more longitudinal decline in global cognitive performance over approximately 3 years

*Not corrected for multiple comparisons; FRAGAMP, Fattori di Rischio Ambientali e Genetici Associati alla Malattia di Parkinson, or Environmental and Genetic Factors in Parkinson's Disease; NET-PD, National Institutes of Health Exploratory Trials in Parkinson's Disease; NMS, non-motor symptoms; NMSS, Non-motor Symptoms Scale; NPF-POP, National Parkinson Foundation-Parkinson's Outcomes Project; UPDRS, Unified Parkinson's Disease Rating Scale

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