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Baseline prevalence and longitudinal evolution of non-motor symptoms in early Parkinson's disease: the PPMI cohort

Tanya Simuni,[1] Chelsea Caspell-Garcia,[2] Christopher S Coffey,[2] Daniel Weintraub,[3] Brit Mollenhauer,[4] Shirley Lasch,[5] Caroline M Tanner,[6] Danna Jennings,[7] Karl Kieburtz,[8] Lana M Chahine,[9] Kenneth Marek[5]

ABSTRACT

Objective To examine the baseline prevalence and longitudinal evolution in non-motor symptoms (NMS) in a prospective cohort of, at baseline, patients with de novo Parkinson's disease (PD) compared with healthy controls (HC).

Methods Parkinson's Progression Markers Initiative (PPMI) is a longitudinal, ongoing, controlled study of de novo PD participants and HC. NMS were rated using the Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Part I score and other validated NMS scales at baseline and after 2 years. Biological variables included cerebrospinal fluid (CSF) markers and dopamine transporter imaging.

Results 423 PD subjects and 196 HC were enrolled and followed for 2 years. MDS-UPDRS Part I total mean (SD) scores increased from baseline 5.6 (4.1) to 7.7 (5.0) at year 2 in PD subjects (p<0.001) versus from 2.9 (3.0) to 3.2 (3.0) in HC (p=0.38), with a significant difference between the groups (p<0.001). In the multivariate analysis, higher baseline NMS score was associated with female sex (p=0.008), higher baseline MDS-UPDRS Part II scores (p<0.001) and more severe motor phenotype (p=0.007). Longitudinal increase in NMS severity was associated with the older age (0.008) and lower CSF Aβ1–42 (0.005) at baseline. There was no association with the dose or class of dopaminergic therapy.

Conclusions This study of NMS in early PD identified clinical and biological variables associated with both baseline burden and predictors of progression. The association of a greater longitudinal increase in NMS with lower baseline Aβ1–42 level is an important finding that will have to be replicated in other cohorts.

Trial registration ClinicalTrials.gov identifier: NCT01141023.

INTRODUCTION

Parkinson's disease (PD) is a progressive neurodegenerative condition associated with a broad range of motor and non-motor symptoms (NMS). A number of NMS, including hyposmia, rapid eye movement behaviour disorder (RBD), depression, anxiety and constipation can occur in the earliest stages of PD and indeed may precede the onset of motor disability,[1–5] theoretically reflecting Braak's staging of PD that demonstrates involvement of the brain stem early in the disease pathological process.[6] The prevalence and clinical correlates of NMS in advanced PD population are well established,[7 8] but NMS are also one of the major factors impairing quality of life in early PD.[9 10] In the last 5 years, there has been a growing body of literature on NMS in early untreated PD, which consistently demonstrates a high prevalence across the spectrum of NMS and generally a lack of correlation with the degree of motor disability.[5 11–14] Only a subset of these studies included a control group, which is essential considering the increasing burden of NMS with ageing. Only two groups have reported longitudinal data on the evolution of NMS in an initially untreated PD population and only one of them had a control group for comparison.[9 11 13 15] Thus, there are limited data from large, controlled, prospective studies on the evolution of NMS in early PD. As was highlighted in the recent review, there is an urgent need to establish the biological underpinnings of NMS early in the disease course.[16]

The aim of this analysis was to systematically explore the prevalence, clinical spectrum, 2-year longitudinal evolution, and biological correlates of NMS in a large group of subjects with early untreated PD (at baseline) compared with healthy controls (HC) enrolled in the Parkinson's Progression Markers Initiative (PPMI).

METHODS

Study design

In brief, PPMI is an ongoing observational, international, multicenter study aimed at identifying serological, genetic, spinal fluid and imaging biomarkers of PD progression in a large cohort of participants with early untreated (de novo) PD at enrolment, compared with HC. The aims and methodology of the study have been published elsewhere and are available at www.ppmi-info.org/study-design.[17] The data used for this paper constitute the analysis of the baseline and 2-year follow-up dataset downloaded 4 January 2016. At the time of data download, all enrolled subjects still in the study had completed at least 2 years of follow-up, with an early study dropout rate of approximately 10%.

Participants

Newly diagnosed, untreated patients with PD (n=423) were enrolled in PPMI. At baseline PD participants were required to: (1) have a recent

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Table 1 Baseline demographics and PD characteristics

Variable	PD subjects (n=423)	Healthy controls (HC) (n=196)	p Value (PD vs HC)
Age			
Mean (SD)	61.7 (9.7)	60.9 (11.2)	0.34
(Min, Max)	(33.5, 84.9)	(30.6, 83.7)	
Missing	0	0	
Age			
<56 years	115 (27.2%)	55 (28.1%)	0.65
56–65 years	152 (35.9%)	76 (38.8%)	
>65 years	156 (36.9%)	65 (33.2%)	
Missing	0	0	
Gender			
Male	277 (65.5%)	126 (64.3%)	0.77
Female	146 (34.5%)	70 (35.7%)	
Missing	0	0	
Education			
<13 years	76 (18.0%)	29 (14.8%)	0.33
13–23 years	344 (81.3%)	166 (84.7%)	
>23 years	3 (0.7%)	1 (0.5%)	
Missing	0	0	
Ethnicity			
Hispanic/Latino	9 (2.1%)	3 (1.5%)	0.62
Not Hispanic/Latino	414 (97.9%)	193 (98.5%)	
Missing	0	0	
Race			
White	391 (92.4%)	182 (92.7%)	0.85
Black/African-American	6 (1.4%)	9 (4.6%)	
Asian	8 (1.9%)	1 (0.5%)	
Other	18 (4.3%)	4 (2.0%)	
Missing	0	0	
Family history of PD			
Family members w/PD	103 (24.4%)	10 (5.1%)	<0.0001
No family members w/PD	319 (75.6%)	186 (94.9%)	
Missing	1	0	
Disease duration (Mon.)			
Mean (SD)	6.7 (6.5)	N/A	N/A
(Min, Max)	(0.4, 35.8)	N/A	
Missing	0	N/A	
Age of PD onset			
Mean (SD)	59.6 (10.0)	N/A	N/A
(Min, Max)	(25.4, 83.0)	N/A	
Missing	8	N/A	
Side most affected			
Left	179 (42.3%)	N/A	N/A
Right	234 (55.3%)	N/A	
Symmetric	10 (2.4%)	N/A	
Missing	0	N/A	
MDS-UPDRS mean (SD) score and subscores			
MDS-UDPRS total score	32.4 (13.1)	4.6 (4.4)	<0.0001
MDS-UDPRS Part I score	5.6 (4.1)	2.9 (3.0)	
MDS-UDPRS Part II score	5.9 (4.2)	0.5 (1.0)	
MDS-UDPRS Part III score	20.9 (8.9)	1.2 (2.2)	
Missing	1	1	
Hoehn and Yahr			
Stage 0	0 (0.0%)	193 (99.0%)	<0.0001
Stage 1	185 (43.7%)	2 (1.0%)	
Stage 2	236 (55.8%)	0 (0.0%)	
Stages 3–5	2 (0.5%)	0 (0.0%)	
Missing	0	1	
Modified Schwab and England Activities of Daily Living Scale			
Mean (SD)	93.2 (5.9)	N/A	N/A
(Min, Max)	(70.0, 100.0)	N/A	
Missing	0	N/A	
TD/non-TD classification			

Continued

Table 1 Continued

Variable	PD subjects (n=423)	Healthy controls (HC) (n=196)	p Value (PD vs HC)
TD	299 (70.9%)	26 (13.3%)	<0.0001
Non-TD	123 (29.1%)	169 (86.7%)	
Missing	1	1	
PIGD score			
Mean (SD)	0.23 (0.2)	0.02 (0.1)	<0.0001
(Min, Max)	(0.0, 1.4)	(0.0, 0.8)	
Missing	1	1	
Tremor score			
Mean (SD)	0.49 (0.3)	0.03 (0.1)	<0.0001
(Min, Max)	(0.0, 1.8)	(0.0, 0.6)	
Missing	1	1	

Report generated on data submitted as of 4 January 2016.
MDS-UPDRS, Movement Disorder Society Unified Parkinson's Disease Rating Scale; PD, Parkinson's disease; PIGD, postural instability gait disorder; TD, tremor dominant.

idiopathic PD diagnosis, (2) be untreated for PD, (3) have a dopamine transporter deficit on the 123-I Ioflupane dopamine transporter (DatScan) on imaging and (4) not have dementia as determined by the site investigator. HC were matched by age and gender and were required to have no significant neurological dysfunction, no first-degree family member with PD and no cognitive impairment based on a Montreal Cognitive Assessment (MoCA) score >26. Participants were recruited at the participating sites and via central recruitment strategies, including online advertising and Fox Trial Finder (https://foxtrialfinder. michaeljfox.org/), the latter an online recruitment tool as previously reported.[18] The study was approved by the institutional review board at each site, and participants provided written informed consent.

STUDY OUTCOMES
For these analyses, NMS were rated with the Movement Disorders Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS)[19] Part I score (0–52) that we subdivided into the subscores for cognitive and psychiatric symptoms ((Q 1.1–1.6) (score range 0–24), sleep (Q 1.7–1.8) (score range 0–8)), pain (Q 1.9 (0–4)), autonomic dysfunction (Q 1.10–1.12 (0–12)) and fatigue (Q 1.13 (0–4)). Each item is rated on a scale of 0–4: (0 none, 1 slight, 2 mild, 3 moderate and 4 severe). The MDS-UPDRS Part I scale has been shown to have strong convergent validity with the Non-Motor Symptoms Scale (NMSS).[20]

Other validated NMS scales available in the PPMI dataset include Montreal Cognitive Assessment (MoCA) for assessment of global cognitive abilities,[21] the 15-item Geriatric Depression Scale (GDS-15),[22] the Scale for Outcomes for PD-autonomic function (SCOPA-AUT),[23] State and Trait Anxiety Scale (STAI),[24] the Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease (QUIP),[25] the Epworth Sleepiness Scale (ESS),[26] the Rapid Eye Movement Behaviour Disorder (RBD) Questionnaire (RBDSQ)[27] and the University of Pennsylvania Smell Identification Test (UPSIT)[28]; the latter was performed only at the baseline. In addition to MoCA, the participants undergo a detailed neuropsychiatric assessment. Of note, we included analysis of the cognitive domain of the MDS-UPDRS I as part of overall NMS, but a detailed analysis of baseline and longitudinal evolution of cognition in the PPMI cohort is out of the scope of this publication and has been previously reported.[29 30]

Other measures included basic demographic variables and the MDS-UPDRS total and subscale scores. Tremor score was calculated as a mean of 11 tremor items (2.10 and 3.15–3.18) and Postural instability Gait Disorder (PIGD) score as a mean of

Table 2 MDS-UPDRS Part I at baseline, year 1 and year 2

Variable	PD subjects				Healthy controls (HC)				p-Values	
	Baseline (n=423)	Year 1 (n=398)	Year 2 (n=380)	p Value (change over time)	Baseline (n=196)	Year 1 (n=185)	Year 2 (n=174)	p Value (change over time)	Group*Visit Interaction	PD versus HC
MDS-UPDRS Part I score										
Mean (SD)	5.57 (4.06)	6.78 (4.60)	7.68 (5.02)	<0.0001	2.94 (2.96)	3.21 (3.21)	3.18 (3.03)	0.3817	<0.0001	N/A*
(Min, Max)	(0.00, 24.00)	(0.00, 29.00)	(0.00, 26.00)		(0.00, 17.00)	(0.00, 16.00)	(0.00, 14.00)			
Missing	1	3	4		1	0	1			
Cognitive impairment										
Normal	315 (74.64%)	279 (71.36%)	242 (64.36%)	0.0007	176 (90.26%)	170 (91.89%)	149 (86.13%)	0.1354	0.5412	<0.0001
Slight	94 (22.27%)	95 (24.30%)	102 (27.13%)		18 (9.23%)	15 (8.11%)	24 (13.87%)			
Mild	13 (3.08%)	15 (3.84%)	25 (6.65%)		1 (0.51%)	0 (0.00%)	0 (0.00%)			
Moderate	0 (0.00%)	2 (0.51%)	7 (1.86%)		0 (0.00%)	0 (0.00%)	0 (0.00%)			
Severe	0 (0.00%)	0 (0.00%)	0 (0.00%)		0 (0.00%)	0 (0.00%)	0 (0.00%)			
Hallucinations and psychosis										
Normal	409 (96.92%)	372 (95.14%)	347 (92.29%)	0.0057	194 (99.49%)	185 (100.00%)	171 (98.84%)	N/A†	N/A†	<0.0001
Slight	13 (3.08%)	19 (4.86%)	24 (6.38%)		1 (0.51%)	0 (0.00%)	2 (1.16%)			
Mild	0 (0.00%)	0 (0.00%)	4 (1.06%)		0 (0.00%)	0 (0.00%)	0 (0.00%)			
Moderate	0 (0.00%)	0 (0.00%)	1 (0.27%)		0 (0.00%)	0 (0.00%)	0 (0.00%)			
Severe	0 (0.00%)	0 (0.00%)	0 (0.00%)		0 (0.00%)	0 (0.00%)	0 (0.00%)			
Depressed mood										
Normal	322 (76.30%)	277 (70.84%)	260 (69.15%)	0.0111	171 (87.69%)	163 (88.11%)	153 (88.44%)	0.9070	0.2815	<0.0001
Slight	85 (20.14%)	86 (21.99%)	81 (21.54%)		21 (10.77%)	16 (8.65%)	16 (9.25%)			
Mild	14 (3.32%)	23 (5.88%)	23 (6.12%)		2 (1.03%)	4 (2.16%)	4 (2.31%)			
Moderate	0 (0.00%)	5 (1.28%)	10 (2.66%)		0 (0.00%)	2 (1.08%)	0 (0.00%)			
Severe	1 (0.24%)	0 (0.00%)	2 (0.53%)		1 (0.51%)	0 (0.00%)	0 (0.00%)			
Anxious mood										
Normal	271 (64.22%)	257 (65.73%)	253 (67.29%)	0.5020	157 (80.51%)	155 (83.78%)	147 (84.97%)	0.2748	0.6480	<0.0001
Slight	130 (30.81%)	101 (25.83%)	95 (25.27%)		34 (17.44%)	24 (12.97%)	23 (13.29%)			
Mild	17 (4.03%)	29 (7.42%)	18 (4.79%)		3 (1.54%)	6 (3.24%)	3 (1.73%)			
Moderate	3 (0.71%)	4 (1.02%)	9 (2.39%)		1 (0.51%)	0 (0.00%)	0 (0.00%)			
Severe	1 (0.24%)	0 (0.00%)	1 (0.27%)		0 (0.00%)	0 (0.00%)	0 (0.00%)			
Apathy										
Normal	351 (83.18%)	301 (76.98%)	278 (73.94%)	0.0002	186 (95.38%)	178 (96.22%)	165 (95.38%)	0.8919	0.3936	<0.0001
Slight	60 (14.22%)	62 (15.86%)	63 (16.76%)		8 (4.10%)	6 (3.24%)	7 (4.05%)			
Mild	10 (2.37%)	25 (6.39%)	27 (7.18%)		1 (0.51%)	1 (0.54%)	1 (0.58%)			
Moderate	0 (0.00%)	3 (0.77%)	7 (1.86%)		0 (0.00%)	0 (0.00%)	0 (0.00%)			
Severe	1 (0.24%)	0 (0.00%)	1 (0.27%)		0 (0.00%)	0 (0.00%)	0 (0.00%)			
Dopamine dysregulation syndrome										
Normal	413 (97.87%)	382 (97.70%)	353 (94.13%)	0.0188	192 (98.46%)	185 (100.00%)	171 (98.84%)	N/A†	N/A†	0.0006
Slight	8 (1.90%)	7 (1.79%)	17 (4.53%)		3 (1.54%)	0 (0.00%)	2 (1.16%)			
Mild	1 (0.24%)	2 (0.51%)	5 (1.33%)		0 (0.00%)	0 (0.00%)	0 (0.00%)			
Moderate	0 (0.00%)	0 (0.00%)	0 (0.00%)		0 (0.00%)	0 (0.00%)	0 (0.00%)			
Severe	0 (0.00%)	0 (0.00%)	0 (0.00%)		0 (0.00%)	0 (0.00%)	0 (0.00%)			
Sleep problems										
Normal	198 (46.92%)	163 (41.69%)	152 (40.43%)	0.0655	110 (56.41%)	94 (50.81%)	95 (54.91%)	0.2950	0.3815	0.0010
Slight	125 (29.62%)	106 (27.11%)	100 (26.60%)		53 (27.18%)	55 (29.73%)	39 (22.54%)			
Mild	62 (14.69%)	79 (20.20%)	80 (21.28%)		19 (9.74%)	23 (12.43%)	24 (13.87%)			
Moderate	26 (6.16%)	35 (8.95%)	31 (8.24%)		10 (5.13%)	11 (5.95%)	13 (7.51%)			
Severe	11 (2.61%)	8 (2.05%)	13 (3.46%)		3 (1.54%)	2 (1.08%)	2 (1.16%)			
Daytime sleepiness										
Normal	213 (50.47%)	150 (38.36%)	118 (31.38%)	<0.0001	127 (65.13%)	117 (63.24%)	102 (58.96%)	0.2332	0.0228	N/A*
Slight	123 (29.15%)	133 (34.02%)	132 (35.11%)		49 (25.13%)	42 (22.70%)	46 (26.59%)			
Mild	84 (19.91%)	106 (27.11%)	119 (31.65%)		18 (9.23%)	25 (13.51%)	25 (14.45%)			
Moderate	2 (0.47%)	1 (0.26%)	4 (1.06%)		1 (0.51%)	1 (0.54%)	0 (0.00%)			
Severe	0 (0.00%)	1 (0.26%)	3 (0.80%)		0 (0.00%)	0 (0.00%)	0 (0.00%)			
Pain and other sensations										
Normal	201 (47.63%)	168 (42.97%)	142 (37.77%)	0.0034	130 (66.67%)	114 (61.96%)	112 (64.74%)	0.4874	0.2124	<0.0001
Slight	168 (39.81%)	151 (38.62%)	171 (45.48%)		53 (27.18%)	55 (29.89%)	46 (26.59%)			
Mild	32 (7.58%)	39 (9.97%)	38 (10.11%)		5 (2.56%)	7 (3.80%)	9 (5.20%)			
Moderate	17 (4.03%)	30 (7.67%)	19 (5.05%)		6 (3.08%)	7 (3.80%)	6 (3.47%)			
Severe	4 (0.95%)	3 (0.77%)	6 (1.60%)		1 (0.51%)	1 (0.54%)	0 (0.00%)			
Urinary problems										

Table 2 Continued

Variable	PD subjects				Healthy controls (HC)				p-Values	
	Baseline (n=423)	Year 1 (n=398)	Year 2 (n=380)	p Value (change over time)	Baseline (n=196)	Year 1 (n=185)	Year 2 (n=174)	p Value (change over time)	Group*Visit Interaction	PD versus HC
Normal	207 (49.05%)	170 (43.48%)	160 (42.55%)	0.0228	148 (75.90%)	139 (75.54%)	133 (76.88%)	0.9005	0.3128	<0.0001
Slight	165 (39.10%)	160 (40.92%)	142 (37.77%)		39 (20.00%)	33 (17.93%)	31 (17.92%)			
Mild	35 (8.29%)	45 (11.51%)	52 (13.83%)		6 (3.08%)	11 (5.98%)	8 (4.62%)			
Moderate	11 (2.61%)	14 (3.58%)	19 (5.05%)		2 (1.03%)	1 (0.54%)	1 (0.58%)			
Severe	4 (0.95%)	2 (0.51%)	3 (0.80%)		0 (0.00%)	0 (0.00%)	0 (0.00%)			
Constipation										
Normal	282 (66.82%)	206 (52.69%)	187 (49.73%)	<0.0001	171 (87.69%)	161 (87.03%)	153 (88.44%)	0.7779	0.0272	N/A*
Slight	109 (25.83%)	139 (35.55%)	135 (35.90%)		21 (10.77%)	22 (11.89%)	18 (10.40%)			
Mild	26 (6.16%)	36 (9.21%)	40 (10.64%)		2 (1.03%)	2 (1.08%)	2 (1.16%)			
Moderate	5 (1.18%)	10 (2.56%)	14 (3.72%)		1 (0.51%)	0 (0.00%)	0 (0.00%)			
Severe	0 (0.00%)	0 (0.00%)	0 (0.00%)		0 (0.00%)	0 (0.00%)	0 (0.00%)			
Lightheadedness										
Normal	311 (73.70%)	274 (70.08%)	244 (64.89%)	0.0061	175 (89.74%)	163 (88.11%)	157 (90.75%)	0.6703	0.2232	<0.0001
Slight	96 (22.75%)	97 (24.81%)	99 (26.33%)		20 (10.26%)	19 (10.27%)	16 (9.25%)			
Mild	12 (2.84%)	18 (4.60%)	23 (6.12%)		0 (0.00%)	3 (1.62%)	0 (0.00%)			
Moderate	3 (0.71%)	2 (0.51%)	9 (2.39%)		0 (0.00%)	0 (0.00%)	0 (0.00%)			
Severe	0 (0.00%)	0 (0.00%)	1 (0.27%)		0 (0.00%)	0 (0.00%)	0 (0.00%)			
Fatigue										
Normal	210 (49.76%)	181 (46.29%)	161 (42.82%)	0.0524	146 (74.87%)	131 (70.81%)	119 (68.79%)	0.2992	0.9097	<0.0001
Slight	165 (39.10%)	144 (36.83%)	138 (36.70%)		44 (22.56%)	46 (24.86%)	48 (27.75%)			
Mild	34 (8.06%)	51 (13.04%)	62 (16.49%)		2 (1.03%)	5 (2.70%)	6 (3.47%)			
Moderate	10 (2.37%)	13 (3.32%)	12 (3.19%)		3 (1.54%)	3 (1.62%)	0 (0.00%)			
Severe	3 (0.71%)	2 (0.51%)	3 (0.80%)		0 (0.00%)	0 (0.00%)	0 (0.00%)			
Cognitive/psychiatric subdomain										
Mean (SD)	1.23 (1.57)	1.53 (1.85)	1.87 (2.27)	<0.0001	0.54 (1.08)	0.48 (1.13)	0.52 (1.01)	0.6261	<0.0001	N/A*
(Min, Max)	(0.00, 13.00)	(0.00, 10.00)	(0.00, 14.00)		(0.00, 8.00)	(0.00, 8.00)	(0.00, 5.00)			
Missing	1	7	4		1	0	1			
Score=0	177 (41.94%)	150 (38.36%)	129 (34.31%)		137 (70.26%)	140 (75.68%)	122 (70.52%)			
One or above	245 (58.06%)	241 (61.64%)	247 (65.69%)	0.0290	58 (29.74%)	45 (24.32%)	51 (29.48%)	0.2169	0.1156	<0.0001
Two or above	134 (31.75%)	148 (37.85%)	164 (43.62%)	0.0001	27 (13.85%)	18 (9.73%)	20 (11.56%)	0.2925	0.0204	N/A*
Sleep subdomain										
Mean (SD)	1.58 (1.49)	1.93 (1.55)	2.13 (1.60)	<0.0001	1.13 (1.30)	1.28 (1.30)	1.33 (1.39)	0.0737	0.0089	N/A*
(Min, Max)	(0.00, 7.00)	(0.00, 8.00)	(0.00, 8.00)		(0.00, 6.00)	(0.00, 5.00)	(0.00, 6.00)			
Missing	1	7	4		1	0	1			
Score=0	123 (29.15%)	87 (22.25%)	70 (18.62%)		83 (42.56%)	63 (34.05%)	64 (36.99%)			
One or above	299 (70.85%)	304 (77.75%)	306 (81.38%)	0.0003	112 (57.44%)	122 (65.95%)	109 (63.01%)	0.1001	0.2159	<0.0001
Two or above	187 (44.31%)	221 (56.52%)	235 (62.50%)	<0.0001	63 (32.31%)	63 (34.05%)	67 (38.73%)	0.2330	0.0259	N/A*
Autonomic subdomain										
Mean (SD)	1.40 (1.37)	1.74 (1.48)	1.99 (1.70)	<0.0001	0.54 (0.81)	0.59 (0.86)	0.51 (0.85)	0.4648	<0.0001	N/A*
(Min, Max)	(0.00, 7.00)	(0.00, 10.00)	(0.00, 8.00)		(0.00, 4.00)	(0.00, 4.00)	(0.00, 5.00)			
Missing	1	7	4		1	0	1			
Score=0	127 (30.09%)	88 (22.51%)	75 (19.95%)		120 (61.54%)	111 (60.00%)	113 (65.32%)			
One or above	295 (69.91%)	303 (77.49%)	301 (80.05%)	0.0002	75 (38.46%)	74 (40.00%)	60 (34.68%)	0.3327	0.0060	N/A*
Two or above	162 (38.39%)	198 (50.64%)	209 (55.59%)	<0.0001	21 (10.77%)	26 (14.05%)	19 (10.98%)	0.4175	0.0432	N/A*

Report generated on data submitted as of 04 January 2016.

p Values for individual Part I items are from logistic models considering response=0 versus any other response.

*PD versus HC comparison is not applicable if test of interaction was significant. A significant test of interaction means the rates of change over time are different between the two groups.

†Test could not be performed because all subjects from one group are in only one category for at least one time point.

MDS-UPDRS, Movement Disorder Society Unified Parkinson's Disease Rating Scale; N/A, not applicable; PD, Parkinson's disease.

five items (2.12, 2.13 and 3.10–3.12).[31] All subjects underwent DatScan measuring the dopamine transporter (DAT) that was analysed according to the imaging technical operations manual (http://ppmi-info.org/). Biological sample tests included cerebrospinal fluid (CSF) biomarkers (β-amyloid 1–42 (Aβ1–42), total tau (T-tau), phosphorylated tau (P-tau$_{181}$) and unphosphorylated total α-synuclein (α-syn)) in all participants. The details of sample collection, processing and biomarker analyses have been previously reported.[32] These measures are currently available only for the baseline and 12 months follow-up samples. Once participants start dopaminergic therapy (DT), the dose is reported as cumulative levodopa equivalent daily dose (LEDD) as well as LEDD by DT subclasses.[33]

STATISTICAL METHODS

All statistical analyses were performed using SAS V.9.4 (SAS Institute, Cary, North Carolina, USA). X^2 or t-tests were used to compare baseline demographics and PD characteristics between groups. Generalised linear mixed (GLM) models were used to test for changes in various non-motor scores over time separately in each group and test for differences between groups over time. In the latter models, an interaction for visit and group was tested

before testing for a group difference over time. GLM models were also used to compare rates of progression among the three NMS subdomain scores over time. Repeated-measures linear mixed models were used to examine the impact of PD medications on NMS total and subdomain scores over time, in the subset of PD subjects who started treatment by year 1. Since no PD subjects were treated at baseline, only year 1 and year 2 time points were included in these models, while adjusting for baseline NMS score.

Linear models were used to examine the univariate and multivariable relationships between baseline demographic, clinical and biological predictors and either baseline NMS score or 2 year change in NMS score. Any variables with univariate associations with p-values <0.20 were included in a multivariable model, and a backwards selection process was used to remove variables individually until all remaining variables were significant at the 0.10 level. Additionally, linear models were used to examine whether baseline NMS total or subdomain scores were predictive of 2 year changes in the following motor disability scores: MDS-UPDRS motor score, tremor and PIGD scores.

Finally, logistic generalised estimating equations (GEE) were used to find estimates of time for each MDS-UPDRS Part 1 item in PD subjects, using a cut-off score of 2 (mild) or above for each item. A significance level of p=0.01 was used as the cut-off to account for multiple comparisons. A more formal method of adjustment for multiple comparisons was not used, as the authors felt this would have been too stringent given the exploratory nature of these analyses. See online supplementary file 1 for further details on the statistical analysis.

RESULTS

There were 423 PD subjects and 196 HC at baseline, and 2-year data were available for 380 PD and 174 HC subjects, with the decrease in sample size due to early study terminations. Baseline demographics and PD characteristics of the cohort are presented in table 1. MDS-UPDRS Part I total mean (SD) scores increased from baseline 5.6 (4.1) to 7.7 (5.0) at year 2 in PD subjects (p<0.001) versus from 2.9 (3.0) to 3.2 (3.0) in HC (p=0.38), with a significant difference between the groups in rates of change over time (p<0.001) (table 2). There was a significant increase over time in every MDS-UPDRS Part I subscore in PD but not HC. The most common NMSs in the PD cohort at baseline (present in >25% based on MDS-UPDRS responses) were sleep dysfunction (53%), pain and other sensation (52%), fatigue (50%), urinary problems (51%), excessive daytime sleepiness (EDS) (50%), anxiety (36%), constipation (33%) and fatigue (50%), though the majority of these were rated as slight (score=1) with a modest increase to mild severity (score=2) in years 1 and 2 (table 2). Sleep dysfunction and daytime sleepiness were the only NMS symptoms with the score of 2 or more in more than 10% of PD participants at baseline. Interestingly, the sleep problems score (Q 1.7) did not change significantly over time while EDS did increase.

Figure 1 shows the probability of being positive (score of 2 or above) for each MDS-UDPRS Part 1 subdomain over time, while the inset table shows the ORs for a 1-year increase in follow-up time compared with baseline. Sleep and autonomic subdomains showed similar rates of change over time, and both subdomains showed greater changes over time compared with the cognitive subdomain. However, there was not sufficient evidence to conclude that the rates were significantly different (p=0.29).

We then analysed evolution of the NMS in PD versus HC using individual domain NMS scales (table 3). Consistent with

the MDS-UPDRS data, there was a significant longitudinal worsening in the scores of global cognition (MoCA), depression (GDS-15), autonomic dysfunction (SCOPA-AUT), and impulse control disorders (QUIP) in PD subjects, while HC worsened only in cognition and trait anxiety (STAI). There was a significant difference in the rate of change of SCOPA-AUT and QUIP between PD subjects (worse) and HC. As per statistical model, the overall PD vs HC group difference was reported only for variables that did not have significant group/visit interactions (table 3).

Variables associated with NMS at baseline, as measured by MDS-UPDRS Part I score, in the PD cohort are shown in table 4. The following baseline variables were significantly associated with the higher NMS score in the multivariate analysis model: female sex (p=0.008), higher MDS-UPDRS Part II scores (p<0.0001) and PIGD subscore (p=0.007). There was also a non-significant association (p=0.06) for higher t-tau/Aβ1–42 ratio predicting total NMS. There was no association with the level of CSF α-synuclein (p=0.44). There was no association of NMS with the degree of motor disability as measured by MDS-UPDRS Part III score, degree, distribution or laterality of presynaptic loss of dopaminergic function as measured by a DatScan. When the same multivariate statistical model was applied for the analysis of the baseline predictors of the longitudinal change of NMS, only older age at enrolment (p=0.008) and lower Aβ1–42 (p=0.005) were significant (table 5).

Given the substantial literature on the potential impact of DT on manifestations of different domains of NMS, we ran a number of analyses. We first compared the degree of change in NMS in treated (n=306) versus untreated (n=69) PD subjects at 2 years and there was no significant difference (p=0.42) (data not shown). We then explored the impact of cumulative dose of DT and specific classes of DT (both expressed as LEDD)[33] on progression of NMS in the subset of treated PD subjects and there were no significant differences (see table 1 in the online supplementary file 1), though LEDD was low overall, 292 (222) mg/day at year 1 and 420 (295) mg/day at year 2. We reran the latter analysis looking at subdomains of NMS, specifically cognition, sleep and autonomic dysfunction, and there was no significant impact of DT on any NMS subdomains.
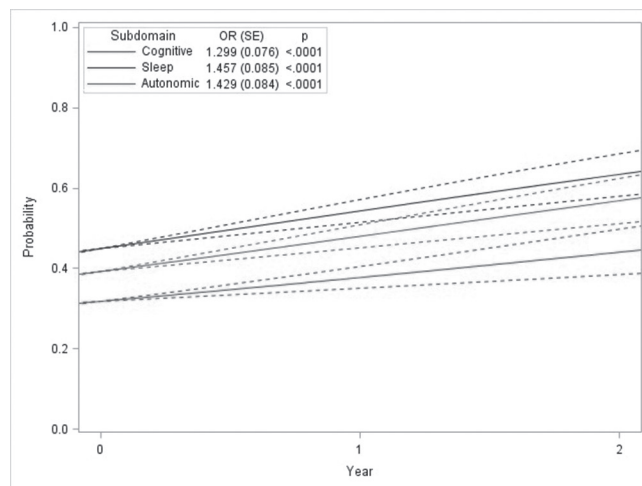

Figure 1 Probabilities (95% CI) and ORs of progression rates for non-motor symptom (NMS) subdomains. NMS domains are defined as Movement Disorder Society Unified Parkinson's Disease Rating Scale Part I subscores as outlined in the publication narrative.

Table 3 Non-motor scores at baseline, year 1 and year 2

Variable	PD subjects				Healthy controls (HC)				p Values	
	Baseline (n=423)	Year 1 (n=398)	Year 2 (n=380)	p-Value (change over time)	Baseline (n=196)	Year 1 (n=185)	Year 2 (n=174)	p-Value (change over time)	Group*Visit interaction	PD versus HC
MoCA										
Mean (SD)	27.13 (2.32)	26.30 (2.83)	26.26 (3.16)	<0.0001	28.23 (1.11)	27.27 (2.19)	27.25 (2.34)	<0.0001	0.8095	<0.0001
(Min, Max)	(17.00, 30.00)	(15.00, 30.00)	(9.00, 30.00)		(26.00, 30.00)	(20.00, 30.00)	(21.00, 30.00)			
Missing	3	6	8		0	0	1			
GDS										
Mean (SD)	2.32 (2.44)	2.57 (2.92)	2.63 (2.87)	0.0049	1.29 (2.10)	1.41 (2.36)	1.16 (1.92)	0.3403	0.1341	<0.0001
(Min, Max)	(0.00, 14.00)	(0.00, 15.00)	(0.00, 15.00)		(0.00, 15.00)	(0.00, 15.00)	(0.00, 12.00)			
Missing	0	3	5		0	0	0			
SCOPA-AUT										
Mean (SD)	9.51 (6.18)	10.92 (6.44)	11.53 (6.56)	<0.0001	5.83 (3.69)	5.84 (4.40)	6.04 (4.37)	0.8642	<0.0001	NA*
(Min, Max)	(0.00, 39.00)	(0.00, 45.00)	(0.00, 42.00)		(0.00, 20.00)	(0.00, 22.00)	(0.00, 22.00)			
Missing	8	8	9		2	1	1			
STAI—state subscore										
Mean (SD)	32.96 (10.24)	32.45 (10.02)	32.48 (10.09)	0.2572	28.02 (8.03)	27.43 (8.59)	27.94 (8.67)	0.5887	0.9003	<0.0001
(Min, Max)	(20.00, 76.00)	(20.00, 77.00)	(20.00, 76.00)		(20.00, 58.00)	(20.00, 64.00)	(20.00, 78.00)			
Missing	1	3	4		0	0	0			
STAI—trait subscore										
Mean (SD)	32.37 (9.45)	32.69 (9.68)	32.58 (9.55)	0.1596	29.11 (7.47)	28.78 (8.77)	28.00 (7.27)	0.0041	0.0282	NA*
(Min, Max)	(20.00, 63.00)	(20.00, 73.00)	(20.00, 66.00)		(20.00, 53.00)	(20.00, 64.00)	(20.00, 58.00)			
Missing	1	3	4		0	0	0			
Epworth Sleepiness Scale (ESS)										
Negative (less than 10)	357 (84.40%)	329 (83.29%)	290 (77.33%)	0.4782	171 (87.69%)	165 (89.19%)	151 (86.78%)	0.6304	0.3868	0.0145
Positive (10 or above)	66 (15.60%)	66 (16.71%)	85 (22.67%)		24 (12.31%)	20 (10.81%)	23 (13.22%)			
Missing	0	3	5		1	0	0			
REM sleep behaviour disorder (RBDQ)										
Negative (less than 5)	261 (62.14%)	256 (65.14%)	218 (58.13%)	0.4137	157 (80.10%)	150 (81.08%)	145 (83.33%)	0.5163	0.1060	<0.0001
Positive (five or above)	159 (37.86%)	137 (34.86%)	157 (41.87%)		39 (19.90%)	35 (18.92%)	29 (16.67%)			
Missing	3	5	5		0	0	0			
QUIP										
No disorders	335 (79.38%)	342 (86.58%)	300 (79.79%)	0.0025	160 (81.63%)	149 (80.54%)	145 (83.33%)	0.5375	0.0135	NA*
Any one or more disorders	87 (20.62%)	53 (13.42%)	76 (20.21%)		36 (18.37%)	36 (19.46%)	29 (16.67%)			
Missing	1	3	4		0	0	0			
Age-adjusted/sex-adjusted UPSIT										
Normosmia	39 (9.22%)	NA	NA	NA	122 (62.24%)	NA	NA	NA	NA	<0.001†
Hyposmia	237 (56.03%)	NA	NA		69 (35.20%)	NA	NA			
Anosmia	147 (34.75%)	NA	NA		5 (2.55%)	NA	NA			
Missing	0				0					

See text for the description of the scales. Higher scores are worse for GDS, SCOPA-AUT, STAI, ESS, RBDQ and QUIP. Higher scores are better for MoCA.
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*PD versus HC comparison is not applicable if test of interaction was significant. A significant test of interaction means the rates of change over time are different between the two groups.
†UPSIT p-value comes from a X^2 test.
GDS, Geriatric Depression Scale; MoCA, Montreal Cognitive Assessment; PD, Parkinson's disease; N/A, not applicable; QUIP, Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease; REM, rapid eye movement; SCOPA-AUT Scale for Outcomes for Parkinson disease-autonomic function; STAI, State and Trait Anxiety Scale; UPSIT, University of Pennsylvania Smell Identification Test.

We also ran analyses to assess the impact of baseline NMS total and subdomain scores on rate of change of motor disability (MDS-UPDRS Part III), as well as tremor and PIGD scores, and did not find an association (see table 2 in the online supplementary file 1).

DISCUSSION

Our study represents one of the largest observational studies of the baseline prevalence and longitudinal evolution of NMS in participants with newly diagnosed, at baseline untreated, PD compared with non-PD controls. Consistent with the prior reports,[5 11–15] our data demonstrate a higher NMS burden and a significant increase over 2 years in NMS in early at baseline untreated PD compared with HC. Our data demonstrate high prevalence and significant change over time but mild severity overall in total NMS scale over time (5.6 (4.1) vs 7.7 (5.0) (range 0–52) (p<0.0001)). We also affirm prior reports that progression of NMS is not associated with the dose or class of DT.[9] Our preplanned analysis was focused on overall NMS burden. Detailed analysis of the predictors of progression of specific cognitive tests or domains in the PPMI cohort is beyond the scope of this publication and has been recently published.[34]

There are a number of novel aspects of the study to be highlighted. This is to our knowledge the largest controlled longitudinal study of the evolution of NMS in early untreated PD versus HC. Erro et al reported initially 2 year and more recently 4-year longitudinal data on the baseline prevalence and longitudinal evolution of NMS in a cohort of 91 patients with PD

Table 4 Baseline predictors of baseline NMS* in PD subjects

Variable	Univariate analysis		Number of observations missing	Multivariable analysis	
	Parameter estimate (95% CI)	p-Value		Parameter estimate (95% CI)	p-Value
Age	0.022 (−0.018 to 0.063)	0.2760	0	–	–
Gender (male)	−0.828 (−1.644 to 0.013)	0.0465	0	−0.952 (−1.659 to 0.245)	0.0084
Education (<13 years)	−0.491 (−1.503 to 0.521)	0.3409	0	–	–
Ethnicity (hispanic)	−0.472 (−3.166 to 2.221)	0.7305	0	–	–
Race (white)	−0.833 (−2.302 to 0.635)	0.2651	0	–	–
Family history of PD	0.020 (−0.887 to 0.927)	0.9656	1	–	–
Age-adjusted/sex-adjusted UPSIT (Anosmia)	0.832 (0.019 to 1.645)	0.0449	0	NS	NS
MDS-UPDRS Part II Score	0.497 (0.417 to 0.577)	<0.0001	0	0.443 (0.351 to 0.534)	<0.0001
MDS-UDPRS Part III Score	0.091 (0.048 to 0.134)	<0.0001	0	NS	NS
Modified Schwab and England Activities of Daily Living Scale	−0.209 (−0.273 to 0.146)	<0.0001	0	NS	NS
Hoehn and Yahr (Stage 1)	−1.002 (−1.780 to 0.223)	0.0118	0	NS	NS
TD/non-TD classification	−1.382 (−2.228 to 0.536)	0.0014	0	Not included	Not included
PIGD score	6.522 (4.896 to 8.149)	<0.0001	0	2.358 (0.645 to 4.072)	0.0071
Tremor score	0.857 (−0.371 to 2.084)	0.1708	0	NS	NS
Side most affected (Left)	−0.038 (−0.765 to 0.688)	0.9172	0	–	–
Disease duration	0.033 (−0.028 to 0.093)	0.2870	0	–	–
Age of PD onset	0.021 (−0.019 to 0.060)	0.3027	8	–	–
Contralateral caudate	−0.698 (−1.400 to 0.003)	0.0509	5	NS	NS
Ipsilateral caudate	−0.460 (−1.122 to 0.202)	0.1725	5	Not included	Not included
Contralateral putamen	0.162 (−1.289 to 1.613)	0.8262	5	–	–
Ipsilateral putamen	−0.412 (−1.436 to 0.612)	0.4299	5	–	–
A-Beta	−0.001 (−0.005 to 0.002)	0.4458	11	–	–
t-tau	0.002 (−0.001, to 0.005)	0.2257	15	–	–
p-tau	−0.001 (−0.005 to 0.002)	0.4738	13	–	–
t-tau/A-Beta	0.004 (0.0001 to 0.007)	0.0389	15	0.003 (−0.0001 to 0.006)	0.0611
p-tau/A-Beta	−0.000 (−0.004 to 0.003)	0.7923	13	–	–
p-tau/t-tau	−0.003 (−0.007 to 0.0001)	0.0462	17	NS	NS
α-Synuclein	0.001 (−0.002 to 0.005)	0.4370	11	–	–

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*NMS is defined as MDS-UPDRS Part I Score.

Note: TD/non-TD classification was not included in the multivariable model because tremor and PIGD scores were already being considered.

Similarly, ipsilateral caudate was not included in the multivariable model because contralateral caudate was already being considered.

MDS-UPDRS, Movement Disorder Society Unified Parkinson's Disease Rating Scale; NMS, non-motor symptoms; PD, Parkinson's disease; PIGD, postural instability gait disorder; TD, tremor dominant; UPSIT, University of Pennsylvania Smell Identification Test.

untreated at baseline using the NMS questionnaire,[9] [13] but the study did not include a control group. Similarly, they found that the majority of patients (97.8%) reported at least one NMS at baseline, with limited overall longitudinal change. They did not see a major impact of DT on overall NMS. In their 4-year follow-up data on a subset of that cohort (n=61), they again demonstrated progression of majority of NMS and lack of association with any class of DT or total LEDD, and lack of association with the motor disability as measured by UPDRS III.[9] Thus, both longitudinal studies provide consistent data. However, our data offer an additional important component of comparison to HC as NMS are also related to general ageing. So far, there has been only one other controlled longitudinal study of clinical and biological predictors of PD progression in a baseline de novo PD population.[11] [15] Mollenhauer et al reported a 2-year single centre follow-up study with extensive phenotypic characterisation and biological ascertainment that included MRI and CSF biomarkers. In contrast to our analysis, they did not identify an association of NMS with the CSF measures but the numbers were smaller and the CSF assay was different. That underscores the exploratory nature of the CSF biomarker findings that will require replication in other cohorts.

Another novel aspect is that we included a multivariate analysis of the baseline variables associated with the higher baseline NMS score and baseline predictors of the longitudinal change of NMS. Such analyses are important as they can provide the clues to the biological underpinnings of NMS as well as help with stratification factors or inclusion criteria that may be useful in designing clinical trials. For the analysis of the baseline NMS burden, we identified three variables: female sex (p=0.008), higher MDS-UPDRS II scores (p<0.0001) and PIGD subscore (p=0.007). Association with the PIGD score and lack of association with the motor disability (MDS-UPDRS III) are not surprising and have been reported by others both in advanced PD cohorts and in the de novo PD population (see Marras and Chaudhari[16] for review). Association of specific domains of NMS (depression, cognitive scores) with the female sex in early PD has also been previously reported though the data have been inconsistent (see Picillo et al for review).[35–39]

Association of older age with the higher burden of NMS is not unexpected and has been well established as a risk factor for overall rate of progression of PD disability.[40] In the analysis of the baseline predictors of the longitudinal change of NMS, only two variables were significant, age at the time of analysis but

Table 5 Baseline predictors of change in NMS* from baseline to year 2 in PD subjects

Variable	Univariate analysis		Number of observations missing	Multivariable analysis	
	Parameter estimate (95% CI)	p Value		Parameter estimate (95% CI)	p-Value
Age	0.064 (0.023 to 0.106)	0.0024	0	0.057 (0.015 to 0.099)	0.0078
Gender (male)	0.722 (−0.134 to 1.578)	0.0982	0	NS	NS
Education (<13 years)	0.623 (−0.461 to 1.706)	0.2590	0	–	–
Ethnicity (hispanic)	−2.354 (−5.011 to 0.302)	0.0822	0	NS	NS
Race (white)	0.457 (−1.048 to 1.961)	0.5510	0	–	–
Family history of PD	−0.664 (−1.601 to 0.274)	0.1649	1	NS	NS
Age-adjusted/sex-adjusted UPSIT (anosmia)	0.332 (−0.523 to 1.186)	0.4458	0	–	–
MDS-UPDRS Part II score	0.061 (−0.039 to 0.161)	0.2312	0	–	–
MDS-UDPRS Part III score	0.000 (−0.046 to 0.047)	0.9884	0	—	–
Modified Schwab and England Activities of Daily Living Scale	−0.006 (−0.077 to 0.065)	0.8631	0	–	–
Hoehn and Yahr (Stage 1)	−0.053 (−0.873 to 0.767)	0.8991	0	–	–
TD/non-TD classification	0.236 (−0.665 to 1.137)	0.6067	0	–	–
PIGD score	−0.987 (−2.797 to 0.824)	0.2845	0	–	–
Tremor score	−0.111 (−1.383 to 1.162)	0.8641	0	–	–
Side most affected (left)	0.565 (−0.194 to 1.323)	0.1440	0	NS	NS
Disease duration	0.033 (−0.029 to 0.095)	0.2905	0	–	–
Age of PD onset	0.060 (0.019 to 0.101)	0.0041	7	NS	NS
Contralateral caudate	−0.329 (−1.088 to 0.431)	0.3952	4	–	–
Ipsilateral caudate	−0.530 (−1.224 to 0.164)	0.1341	4	NS	NS
Contralateral putamen	−0.887 (−2.565 to 0.791)	0.2993	4	–	–
Ipsilateral putamen	−1.298 (−2.381 to 0.215)	0.0189	4	NS	NS
A-Beta	−0.005 (−0.009 to 0.002)	0.0024	9	−0.005 (−0.008 to 0.002)	0.0046
t-tau	−0.003 (−0.006 to 0.001)	0.0966	13	NS	NS
p-tau	−0.001 (−0.004 to 0.003)	0.6422	11	–	–
t-tau/A-Beta	−0.001 (−0.004 to 0.003)	0.6951	13	–	–
p-tau/A-Beta	0.002 (−0.001 to 0.006)	0.2024	11	–	–
p-tau/t-tau	0.001 (−0.002 to 0.005)	0.5213	15	–	–
α-Synuclein	−0.002 (−0.005 to 0.002)	0.3010	9	–	–

Report generated on data submitted as of 4 January 2016.

*NMS is defined as MDS-UPDRS Part 1 score.

MDS-UPDRS, Movement Disorder Society Unified Parkinson's Disease Rating Scale; NMS, non-motor symptoms; PD, Parkinson's disease;N.S, not significant; PIGD, postural instability gait disorder; TD, tremor dominant; UPSIT, University of Pennsylvania Smell Identification Test.

not age of PD onset and lower CSF Aβ1–42. Interestingly, age was not significantly associated with baseline severity of NMS but was with the rate of progression. The opposite was true for female sex, as that was not a significant predictor of the longitudinal change in NMS but was associated with the baseline NMS severity. Difference in the variables associated with the baseline NMS burden versus longitudinal progression of NMS might reflect difference in biological underpinnings of the disease trait versus state and deserve further exploration with the longer follow-up and validation in other cohorts.

The major novel aspect of this study is the inclusion of biomarker data. We did not find an association of baseline burden or rate of NMS progression with the DAT imaging. That could be related to the hypothesis that NMS are largely driven by non-dopaminergic pathways or alternatively that the analysis did not tease out specific domains of NMS that could be more linked to the degree of dopamine deficiency. In that regard, it would be instructive to also have serotonin and cholinergic ligand imaging, but these are not part of the dataset.

In the multivariate analysis of CSF biomarkers, we identified a trend for higher t-tau/Aβ1–42 ratio (p=0.06) association with NMS at baseline and lower level of Aβ1–42 (p=0.005) association with longitudinal progression of NMS. There was no association with α-synuclein. The role of β-amyloid and tau protein

as biomarkers in PD is not well established, but number of publications including a pilot PPMI data analysis reported reduction of levels of CSF Aβ1–42, t-tau or p-tau in patients with PD with or without dementia compared with HC.[30 32 41–44] A lower level of Aβ1–42 was associated with the baseline level of somnolence in the PPMI cohort, though again at a marginal level of significance.[45] One possibility is that the low CSF Aβ1–42 reflects the presence of early stages of cortical Aβ1–42 deposition in PD, manifesting with various NMS, analogous to the occurrence of various neuropsychiatric symptoms and sleep disturbances prior to the diagnosis of Alzheimer's dementia.[46 47] It remains to be determined if the association with the lower level of Aβ1–42 will persist with longer follow-up and if an association with α-synuclein will emerge at more advanced staged of PD.

There are a number of study limitations to be acknowledged. PPMI cohort might not be reflective of the general PD population, as based on the fairly demanding nature of the study ascertainments the study attracts younger and relatively cognitively intact at baseline. Indeed, the age of the cohort is younger than the average age of PD onset though is consistent with the cohorts recruited in majority of the disease modification trials. The same can be true of the healthy control cohort that might be representative of the 'super controls' though inclusion criteria for HC were fairly broad aside from the cognitive cut-offs. Our results will have to be confirmed in longer duration follow-up

that is planned. In addition, NMS assessment was based on MDS-UPDRS Part 1 and selected domain-specific scales. As such it lacked in-depth assessment of some domains like sleep or RBD with polysomnography, comprehensive objective assessment of autonomic dysfunction, or other specific domain scales and could have missed other variables. Lastly, NMS assessments were based on PD-specific scales and might not be optimal for assessment of HC cohort. Despite that, we believe that PPMI has a sufficiently rich ascertainment of the NMS domain of PD and HC to provide meaningful data analysis. In conclusion, our study confirms previous reports of high prevalence and significant longitudinal increase even over a relatively short time period of essentially all domains of NMS in early at baseline untreated PD participants. Increase of overall NMS in early PD was not linked to either cumulative dose or specific classes of DT, though it remains to be determined if this will remain true with the increase of the LEDD as the disease progresses. Association of NMS progression with the lower baseline levels of $A\beta 1-42$ is intriguing and can contribute to the knowledge of the potential biological underpinnings of NMS in PD, though this will have to be replicated in other cohorts. Further longitudinal data will establish impact of early NMS on the long-term progression of PD disability and could be helpful for subtyping of PD population and potentially for stratification into clinical trial.

Author affiliations
[1]Department of Neurology, Northwestern University Feinberg School of Medicine, Chicago, Illinois, USA
[2]Department of Biostatistics, University of Iowa, Iowa City, Iowa, USA
[3]University of Pennsylvania School of Medicine and the Parkinson's Disease and Mental Illness Research, Education and Clinical Centers (PADRECC and MIRECC), Philadelphia Veterans Affairs Medical Center, Philadelphia, Pennsylvania, USA
[4]Center of Parkinsonism and Movement Disorders Paracelsus-Elena Klinik Kassel, University Medical Center Goettingen, Kassel, Germany
[5]Institute for Neurodegenerative Disorders, New Haven, Connecticut, USA
[6]University of California San Francisco, San Francisco, California, USA
[7]Eli Lilly and Company, Indianapolis, Indiana, USA
[8]University of Rochester Medical Center, Rochester, New York, USA
[9]University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania, USA

Collaborators The Parkinson's Progressive Marker Initiative—PPMI: PPMI Steering Committee: Kenneth Marek, MD (Principal Investigator); Shirley Lasch, MBA; Caroline Tanner, MD, PhD (Site Investigator); Tanya Simuni, MD (Site Investigator); Christopher Coffey, PhD (Statistics Core, PI); Karl Kieburtz, MD, MPH (Clinical Core, PI); Renee Wilson; Brit Mollenhauer, MD (Bioanalytics Core, co-PI; Site Investigator); Douglas Galasko, MD (Bioanalytics Core, co-PI; Site Investigator); Tatiana Foroud, PhD (Genetics Coordination Core and Biorepository, PI); Lana Chahine, MD (Site Investigator); Andrew Siderowf, MD, MSCE; John Seibyl, MD (Imaging Core, PI); Arthur Toga, PhD (Bioinformatics Core, PI); Andrew Singleton, PhD (Genetics Core, PI); Daniel Weintraub, MD (Cognitive and Behavioral); John Trojanowski, MD, PhD; Leslie Shaw, PhD; Duygu Tosun-Turgut, PhD (DTI, PI); Kathleen Poston, MD, MS (fMRI, PI); Susan Bressman, MD; Kalpana M Merchant, MD; Werner Poewe, MD (Site Investigator); Todd Sherer, PhD; Sohini Chowdhury; Mark Frasier, PhD; Catherine Kopil, PhD; Anna Naito, PhD and Vanessa Arnedo were responsible for the scientific rationale, study design, site selection, logistics, data management and analysis planning for the study. PPMI Study Cores: Clinical Coordination Core: Ray Dorsey, PhD; Cynthia Casaceli, MBA—The Clinical Coordination Core was responsible for study concept or design and analysis or interpretation of clinical including collection, tracking and performance of quality control. Imaging Core: Nichole Daegele; Justin Albani—The Imaging Core was responsible for study concept or design and analysis or interpretation of imaging data. Statistics Core: Chelsea Caspell-Garcia; Liz Uribe, MS; Eric Foster; Jeff Long, PhD; Nick Seedorff—The Statistics Core led the statistical analyses and supported study concept or design and analysis or interpretation of data. Bioinformatics Core: Karen Crawford, MLIS—The Bioinformatics core was responsible for concept or design and maintained the PPMI study database to contribute to the support of the analytic analysis and data quality. Bio Repository: Danielle Elise Smith; Paola Casalin; Giulia Malferrari—The Biorepository Core was responsible for study concept or design, analysis or interpretation of biosamples, collection quality and data analysis. Genetics Coordination and Pathology Core: Cheryl Halter; Laura Heathers—The Genetics Coordination Core contributed to study concept or design and analysis or interpretation

of cohort data. PPMI Site Investigators: David Russell, MD, PhD; Stewart Factor, DO; Penelope Hogarth, MD; David Standaert, MD, PhD; Amy Amara, MD, PhD; Robert Hauser, MD, MBA; Joseph Jankovic, MD; Matthew Stern, MD; Shu-Ching Hu, MD PhD; Gretchen Todd; Rachel Saunders-Pullman MD; Irene Richard, MD; Marie H Saint-Hilaire, MD; Klaus Seppi, MD; Holly Shill, MD; Hubert Fernandez, MD; Claudia Trenkwalder, MD; Wolfgang Oertel MD; Daniela Berg, MD; Kathrin Brockman, MD; Isabel Wurster MD; Liana Rosenthal, MD; Yen Tai, MD; Nicola Pavese, MD; Paolo Barone, MD, PhD; Stuart Isaacson, MD; Alberto Espay, MD, MSc; Dominic Rowe, MD, PhD; Melanie Brandabur MD; James Tetrud MD; GraceLiang MD; Alex Iranzo, MD; Eduardo Tolosa MD; Karen Marder, MD; Maria de ArribaSanchez, MD; Leonidis Stefanis, MD, PhD; Maria Jose Marti, MD, PhD; Javier Ruiz Martinez, MD, PhD; Jean-Christophe Corvol, MD; Jan O Assly, MD; Salima Brillman, MD and Nir Giladi, MD were responsible for data collection and contribution to data quality and analysis. PPMI Site Coordinators: Debra Smejdir; Julia Pelaggi; Farah Kausar, PhD; Linda Rees, MPH; Barbara Sommerfield, MSN, RN; Madeline Cresswell; Courtney Blair, MA; Karen Williams; Grace Zimmerman; Stephanie Guthrie, MSN; Ashlee Rawlins; Leigh Donharl; Christine Hunter, RN; Baochan Tran; Abigail Darin; Carly Linder; Marne Baca; Heli Venkov; Cathi-Ann Thomas, RN, MS; Raymond James, RN; Beatrice Heim, MD; Paul Deritis; Fabienne Sprenger, MD; Deborah Raymond; Diana Willeke; Zoran Obradov, CRC; Jennifer Mule; Nancy Monahan; Katharina Gauss; Deborah Fontaine, BSN, MS; Daniel Szpak; Arita McCoy; Becky Dunlop; Laura Marie Payne; Susan Ainscough; Lisbeth Carvajal; Rebecca Silverstein; Kristy Espay; Madelaine Ranola; Elisabet Mondragon Rezola; Helen Mejia Santana; Maria Stamelou, MD, PhD; Alicia Garrido, MD; Stephanie Carvalho, MS; Anne Grete Kristiansen; Krista Specketer Anat Mirlman were responsible for data collection and contribution to data quality. ISAB (Industry Scientific Advisory Board): Maurizio Facheris, MD; Holly Soares, PhD; Mark A Mintun, MD; Jesse Cedarbaum, MD; Peggy Taylor, ScD; Danna Jennings, MD; Lawrence Slieker, MD; Brian McBride, PhD; Colin Watson, PhD; Etienne Montagut, MBA; Zulfiqar Haider Sheikh; Baris Bingol, PhD; Remi Forrat; PabloSardi, PhD; Tanya Fischer, MD, PhD; Alastair D Reith, PhD; Jan Egebjerg, PhD; Lone Frydelund Larsen; Nathalie Breysse, PhD; Didier Meulien, MD; Barbara Saba,MD; Vera Kiyasova, MD, PhD; Chris Min, MD, PhD; Thomas McAvoy, PhD; Robert Umek, PhD; Philip Iredale, PhD; Jeremy Edgerton, PhD; Susan De Santi, PhD;Christian Czech, PhD; Frank Boess, PhD; Jeffrey Sevigny, MD; Thomas Kremer, PhD; Igor Grachev, MD, PhD; Kaplana Merchant, PhD; Andreja Avbersek, MD; Pierandrea Muglia, MD; Alexandra Stewart, MBA; Rene Prashad, PhD and JohannesTaucher, MD were responsible for funding and scientific rationale.

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