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Self-reported physical activity levels and clinical progression in early Parkinson's disease

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ABSTRACT

Introduction: This study investigates longitudinal changes in self-reported physical activity, measured by Physical Activity Scale of the Elderly (PASE), in early Parkinson's disease (PD) and matched healthy control (HC) participants in the Parkinson's Progression Marker Initiative (PPMI) and evaluates associations between physical activity and PD progression.

Methods: PPMI is a prospective, longitudinal study evaluating markers of progression in PD participants who are unmedicated at enrollment. PASE, a self-reported measure of physical activity, was administered to early PD (N = 380) and HC (N = 174). PASE was introduced after study launch and therefore administered at years 2, 3, and 4. PASE scores for PD and HC were compared with t-tests and changes over time were evaluated with generalized estimating equations.

Results: There were no differences in activity levels between PD and HC at any time point. However, PD participants had a longitudinal decrease in PASE from years two to four ($p = 0.034$), while HC did not ($p = 0.89$). In exploratory analyses controlling for age, sex, and disease duration, higher self-reported activity at year 2 were associated with slower progression of motor symptoms ($p = 0.018$), ADL performance ($p < 0.0001$), depression ($p = 0.001$), anxiety ($p = 0.002$), and cognitive decline ($p = 0.016$) over two years. These findings remained significant after adjusting for disease severity.

Conclusion: There are no differences in self-reported physical activity between HC and early PD, but activity levels decline longitudinally in PD. Exploratory analyses show that higher self-reported physical activity is associated with less disease progression. Therefore, interventions to increase physical activity in early PD could potentially modify the disease course.

1. Introduction

Parkinson's disease (PD) is a progressive neurodegenerative disorder with no known disease modifying treatment. PD patients experience motor and non-motor symptoms, including mood disorders, sleep dysfunction, cognitive decline, autonomic dysfunction, and psychosis. For these disabling symptoms, the only available therapies target symptom management. Physical activity improves both motor and non-motor symptoms in PD [1–3], and several large, prospective, epidemiologic studies suggest that higher levels of physical activity are associated with reduced risk of development of PD [4–7]. In disease-manifest PD, higher activity levels are associated with improved quality of life, better motor performance, and less cognitive decline over one year [8] and exercise interventions can improve muscle strength, balance, motor symptoms, quality of life, and cardiorespiratory fitness [2,9]. Unfortunately, some studies show that patients with mild-moderate PD have less physical activity than similarly aged healthy older adults, and activity level declines over time [10–12]. The cause of reduced physical activity is likely multifactorial, with potential contributors including progressive motor symptoms, fear of falling, depression, daytime sleepiness, apathy, cognitive impairment, cessation of driving, lack of self-efficacy (belief in one's capacity to overcome barriers) and unidentified

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factors [13,14].

Longitudinal changes in physical activity in early PD and healthy controls (HC) have not been previously reported and the impact of physical activity levels in early PD on motor and non-motor progression in PD is unknown. We address this knowledge gap by reporting these outcomes in PD and HC participants of the Parkinson's Progression Markers Initiative (PPMI).

2. Methods

The sample was drawn from the Parkinson's Progression Markers Initiative (PPMI) study cohort. The current study reports data collected starting at year 2 because that was the first time point at which the primary outcome (Physical Activity Scale of the Elderly: PASE) was collected. Study aims and methodology have been published elsewhere [15] and are detailed on the PPMI website (http://www.ppmi-info.org/study-design). In brief, PPMI enrolled 423 individuals with de novo PD and 196 HC, across 21 sites. The current study analyzed data from 380 PD participants and 174 HC participants who were available at the 2-year follow up assessments, followed longitudinally.

For PD participants, inclusion at enrollment required: ≥two of three cardinal signs of PD (bradykinesia, rigidity, or rest tremor), diagnosis within two years of enrollment, presence of dopamine transporter deficit on ^{123}I ioflupane SPECT imaging (DaTscan™), no dopaminergic treatment for PD prior to enrollment, and absence of dementia based on site investigator's clinical assessment. Healthy controls were required to have Montreal Cognitive Assessment (MoCA) score > 26 [15].

Exclusion criteria for both PD and HC included medical conditions precluding study participation at investigator discretion or clinically significant MRI abnormality. Family history of PD in a first degree relative was also an exclusion for HC [15].

The study was approved by the institutional review board at each participating site, and written informed consent was obtained from all participants. This study is listed in clincaltrials.gov (NCT01141023). Data used in this analysis were downloaded on January 3, 2017.

2.1. Assessments

Participants were evaluated yearly with the PASE, starting at year 2 after enrollment. The PASE is a validated, self-reported questionnaire assessing the frequency, intensity, and duration of activity over the prior week [16]. This scale has a test-retest reliability of 0.75 and good construct validity [17]. In its validation study, the mean ± SD PASE score among participants aged 65–100 was 102.9 ± 64.1, which decreased with age and was higher in men [17]. The PASE assesses three activity categories: leisure, household chores, and work/volunteering. The leisure subscore includes questions about light activity (reading); light recreational activity (bowling, golf); walking; moderate or vigorous physical activity (tennis, swimming); and muscle strengthening (weight lifting). The household subscore includes questions about light and heavy housework, home repairs, lawn work, gardening, or serving as a caregiver. The work subscore includes questions about hours spent working or volunteering and the amount of physical activity required for work (office work versus manual labor). Higher PASE scores indicate more physical activity. The PASE correlates well with objective measures of physical activity including peak oxygen uptake ($VO2_{peak}$), waist and ankle activity monitors, balance, leg strength, and the 6-min walk [16–18].

All PPMI participants undergo annual motor and non-motor assessments including the Movement Disorders Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) and Hoehn and Yahr (H&Y) stage. For participants on levodopa and/or dopamine agonists, MDS-UPDRS and H&Y were assessed both in the ON state and in the relative medication OFF state, defined as > 6 h after last dose of levodopa or dopamine agonist [15]. The medication ON state is defined as 1–3 h following a dose of levodopa or dopamine agonist. Here, only OFF scores are reported for MDS-UPDRS part III and total and H&Y. The MDS-UPDRS was used to classify participants as tremor dominant (TD) or postural instability/gait disorder (PIGD), as previously described [19]. The modified Schwab and England activities of daily living scale (S&E) was also assessed.

Participants completed an annual neuropsychological battery, which included MoCA, Symbol Digit Modalities Test (SDMT), Semantic fluency (animals, vegetables, fruit), Letter-Number Sequencing (LNS), Hopkins Verbal Learning Test-Revised (HVLT-R; immediate and delayed free recall and recognition), and Benton Judgment-of-Line-Orientation (JOLO) 15-item (split-half) version.

Other non-motor assessments included the Scales for Outcomes in Parkinson's Disease-Autonomic (SCOPA-AUT); Geriatric Depression Scale, 15-item version (GDS-15); Anxiety–State-Trait Anxiety Inventory (STAI); Epworth Sleepiness Scale (ESS); and REM sleep behavior disorder questionnaire (RBDSQ). To evaluate subjective sleep and fatigue, questions 1.7 and 1.13 of the MDS-UPDRS were also used in the analysis. Levodopa equivalent dose (LED) was calculated as previously described [20].

Additionally, all participants were evaluated with DaTscan™ to measure presynaptic dopaminergic dysfunction. Methods of acquisition and analysis are described in the imaging technical operations manual (www.ppmi-info.org) [15].

2.2. Statistical methods

Analyses were performed using SAS 9.4 (SAS Institute Inc., Cary, NC). T-tests and Chi-square tests as appropriate were used to compare year 2 demographics and PD characteristics between groups.

2.2.1. Longitudinal analysis of PD and non-motor characteristics

Summary statistics for PD and Non-Motor characteristics were provided by year. Changes in variables over time were then assessed using Generalized Estimating Equations (GEEs). Models were fit with an autoregressive 1 covariance structure and quasi-likelihood estimation.

2.2.2. Longitudinal analysis of physical activity in PD and HC

Summary statistics for various PASE scores were presented by group and year. T-tests were used to compare variables at each time point while GEEs were used to calculate changes in PASE scores over time.

2.2.3. Univariate analysis with physical activity predictor

Linear models were used to examine univariate relationships between various outcome variables and PASE scores while adjusting for age, gender, and disease duration. Outcome variables included clinical and biological markers.

2.2.4. PASE scores as a predictor of disease severity

If there was not a significant interaction between PASE score and time, models were fit and results attained using GEE with an autoregressive 1 covariance structure. All models were fit with a main effect for PASE and adjusted for age, sex, and disease duration. In secondary analyses, models adjusted for age, sex, disease duration, and motor severity (MDS-UPDRS, part III). Due to the exploratory and hypothesis-generating nature of these analyses, we did not correct for multiple comparisons.

3. Results

3.1. Longitudinal change in physical activity

There were no demographic differences between PD and HC participants (Table 1). Physical activity, as measured by PASE, was not different at any time point between PD and HC, although PD participants had significantly less work-related activity (PASE Work subscore) (Table 2). Longitudinal evaluation over years two to four demonstrates

Table 1
Demographics and PD characteristics at year 2.

Variable	Enrolled Subjects year 2		
	PD Subjects	Healthy Controls	p-value
	(N = 380)	(N = 174)	(PD vs HC)
Age at Year 2			0.461
Mean (SD)	63.55 (9.8)	62.85 (11.3)	
(Min, Max)	(35.5, 86.8)	(32.6, 85.8)	
Missing	3	0	
Gender			0.430
Male	249 (65.5%)	108 (62.1%)	
Female	131 (34.5%)	66 (37.9%)	
Missing	0 (0%)	0 (0%)	
Education			0.852
< 13 Years	64 (16.8%)	26 (14.9%)	
13–23 Years	314 (82.6%)	147 (84.5%)	
> 23 Years	2 (0.5%)	1 (0.6%)	
Missing	0 (0%)	0 (0%)	
Age of PD Onset			N/A
Mean (SD)	59.50 (10.1)	N/A	
(Min, Max)	(25.4, 83.0)	N/A	
Missing	7	N/A	
Disease Duration (Months) at Year 2			N/A
Mean (SD)	31.25 (6.7)	N/A	
(Min, Max)	(24.0, 59.3)	N/A	
Missing	3	N/A	
Side Most Affected			N/A
Left	161 (42.4%)	N/A	
Right	210 (55.3%)	N/A	
Symmetric	9 (2.4%)	N/A	
Missing	0	N/A	

that PD participants become significantly less active over time (decreasing total PASE score), while PASE scores are unchanged over the same duration among HCs. There is no clear PASE subscore that drives the decline in physical activity over time among PD participants. There is no longitudinal change in the subscores among HC participants (Table 2). The longitudinal changes in clinical variables among PD participants, such as motor symptoms and non-motor symptoms, have been reported previously and are included in eTable1 (Supplement).

3.2. Clinical measures associated with physical activity in PD

The only demographic variable associated with PASE at year 2 was age, with higher PD participant age associated with less physical activity, such that each year older age was associated with 3.03 points lower PASE total score (95% CI: 4.2, −1.9; $p < 0.0001$) (eTable 2 in Supplement). Analyses performed to determine the influence of physical activity at year 2 on disease progression demonstrated that, after adjusting for age, sex, and disease duration, higher PASE score (more physical activity) was associated with less progression of motor symptoms: lower MDS-UPDRS total, part II, and part III scores, lower walking and balance score, lower PIGD score, and higher S&E ADL score (Table 3). Further, higher physical activity was associated with better performance on semantic fluency and SDMT and improved mood (GDS and STAI) (Table 3). Higher PASE scores were also associated with higher MoCA, and there was a significant PASE × time interaction, with PASE significantly associated with higher MoCA scores between years 2 and 4. These findings remained significant after adjusting for MDS-UPDRS part III score (Table 4) and a significant PASE × time interaction emerged for sleep quality following this adjustment, showing that after controlling for motor severity, higher levels of physical activity were associated with better sleep quality over time. There were no associations between PASE total score and dopamine transporter binding, LED, or subjective measures of daytime sleepiness, fatigue, or autonomic function.

When evaluating the association between PASE subscores and rate of progression of PD, higher leisure subscore was associated with lower MDS-UPDRS part II, better performance on SDMT, and improved mood (GDS and STAI) (eTable 3 in Supplement). Further, there was a

Table 2
Comparison of PASE score at year 2, year 3, and year 4 in Parkinson's disease and healthy control participants.

Variable	Year 2			Year 3			Year 4			Change over time	
	PD	HC	p-value[a]	PD	HC	p-value[a]	PD	HC	p-value[a]	p-value	p-value
	(N = 380)	(N = 174)		(N = 366)	(N = 167)		(N = 278)	(N = 136)		**(PD)**	**(HC)**
PASE Score			0.994			0.276			0.263	**0.034**	0.894
Mean (SD)	171.85 (100.7)	171.95 (85.2)		162.87 (98.4)	172.61 (76.7)		160.97 (104.0)	172.78 (92.8)			
(Min, Max)	(2.2, 613.4)	(27.2, 445.2)		(0.0, 589.2)	(0.0, 395.9)		(2.3, 734.0)	(15.0, 509.1)			
Missing	104	88		15	13		5	0			
PASE Leisure Score			0.506			0.702			0.606	0.318	0.755
Mean (SD)	54.97 (60.1)	50.18 (52.2)		50.94 (56.5)	48.94 (47.0)		52.01 (57.7)	48.93 (55.7)			
(Min, Max)	(0.0, 462.4)	(0.0, 292.2)		(0.0, 418.2)	(0.0, 305.3)		(0.0, 323.0)	(0.0, 338.8)			
Missing	104	88		15	14		5	0			
PASE Household Score			0.265			0.094			0.619	0.349	0.466
Mean (SD)	86.86 (43.0)	92.64 (38.2)		83.65 (45.1)	90.64 (38.2)		85.51 (44.6)	87.72 (37.2)			
(Min, Max)	(0.0, 171.0)	(0.0, 171.0)		(0.0, 171.0)	(0.0, 171.0)		(0.0, 171.0)	(0.0, 171.0)			
Missing	104	88		15	13		5	0			
PASE Work Score			0.893			0.329			**0.022**	0.063	0.786
Mean (SD)	30.02 (53.9)	29.13 (53.4)		28.29 (54.0)	33.35 (52.6)		23.44 (50.6)	36.13 (56.4)			
(Min, Max)	(0.0, 195.0)	(0.0, 240.0)		(0.0, 240.0)	(0.0, 192.0)		(0.0, 240.0)	(0.0, 180.0)			
Missing	104	88		15	13		5	0			

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Bold values indicates: $p < 0.05$.
[a] PD versus HC.

Table 3
Impact of baseline (year 2) PASE score on the Rate of Progression of Disability Over Years 2–4 in PD.

Variable	# Subjects	Estimate	Univariate
	Missing	Value (95% CI)	p-value
MDS-UPDRS Total Score	10	−0.0167 (−0.028, −0.006)	**0.003**
MDS-UPDRS Part I	10	−0.0021 (−0.006, 0.001)	0.231
MDS-UPDRS Part II	10	−0.0058 (−0.009, −0.003)	**< .0001**
MDS-UPDRS Part III (Motor Exam)	10	−0.0092 (−0.017, −0.002)	**0.018**
MDS-UPDRS Part IV	10	0.0015 (−0.0004, 0.003)	0.124
MDS-UPDRS Walking and Balance	11	−0.0019 (−0.003, −0.0004)	**0.011**
TD Score	10	−0.0001 (−0.0004, 0.0001)	0.275
PIGD score	10	−0.0004 (−0.001, −0.0001)	**0.004**
Postural Instability	127	−0.0035 (−0.009, 0.002)	0.196
Modified Schwab & England ADL	10	0.0119 (0.006, 0.0175)	**< .0001**
MOCA	10	*	*
HVLT Total Score	10	0.0013 (−0.005, 0.007)	0.671
Benton Judgement of Line Orientation	10	0.0007 (−0.001, 0.002)	0.380
Semantic Fluency	10	0.0087 (0.002, 0.0155)	**0.012**
Letter Number Sequencing	10	0.0001 (−0.0019, 0.0020)	0.933
Symbol Digit Modalities	10	0.0118 (0.0054, 0.0182)	**0.0003**
MDS-UPDRS Part I Sleep	10	−0.0002 (−0.0015, 0.0012)	0.779
MDS-UPDRS Part I Fatigue	10	−0.0010 (−0.0024, 0.0005)	0.207
Epworth Sleepiness Scale Score	10	0.0000 (−0.0029, 0.0030)	0.977
REM Sleep Behavior Disorder	10	0.0008 (−0.0006, 0.0022)	0.267
SCOPA-AUT Total Score	10	0.0016 (−0.0031, 0.0062)	0.508
GDS	10	−0.0031 (−0.0050, −0.0012)	**0.001**
State-Trait Anxiety Index	10	−0.0174 (−0.0284, −0.0065)	**0.002**
Contralateral Caudate	10	0.0003 (−0.0003, 0.0009)	0.374
Ipsilateral Caudate	10	0.0007 (−0.0001, 0.0015)	0.079
Contralateral Putamen	10	−0.0000 (−0.0002, 0.0001)	0.619
Ipsilateral Putamen	10	−0.0001 (−0.0005, 0.0002)	0.439
LED	10	−0.0244 (−0.2527, 0.2040)	0.834
PASE Score by Time Interaction Effects			
MOCA			**0.007****
Year 2 to Year 3	10	−0.00012 (−0.00354, 0.00330)	0.945**
Year 2 to Year 4	10	0.00361 (0.00067, 0.00656)	**0.016****

Note: If estimate = * then evidence of a significant interaction effect over time. Otherwise, not enough evidence to support an interaction.
**p-value is for an overall PASE Score and time interaction; Note: Analyses adjust for age, gender, and disease duration. Report Generated on Data Submitted as of: 03Jan2017.
Bold values indicates: $p < 0.05$.

significant PASE leisure × time interaction for S&E, MoCA, and the semantic fluency test. Similar to the PASE total score, higher PASE household subscore was associated with less motor severity progression (MDS-UPDRS total, parts I, II, III, and walking and balance score, PIGD score, and higher S&E score) (eTable 4 in Supplement). Higher household subscore was also associated with better performance on cognitive measures including MoCA, Benton judgment of line orientation, semantic fluency, and SDMT as well as lower scores on the mood measures. The PASE work subscore was only associated with change in the walking and balance score, and showed a significant PASE work subscore × time interaction for SDMT, being significant for year 2 to year 4 (eTable 5 in Supplement).

4. Discussion

To our knowledge, this multisite, international study is the first to compare changes in self-reported levels of physical activity over time in a large cohort of early PD and HC participants. Although there were no differences in physical activity at baseline (year 2), as measured by PASE, between early PD and HC, only the PD participants had decline in PASE scores longitudinally over years two to four of the study. Further, exploratory analyses demonstrate that higher physical activity levels at the time of initial assessment (year 2) were associated with less progression of disease severity, cognition decline, and mood symptoms in PD patients. These findings indicate that interventions to increase physical activity early in the course of PD could have beneficial effects on multiple facets of the disease, including motor and non-motor symptoms.

The PPMI cohort is unique in that it includes participants with de novo, un-medicated PD at the time of enrollment. While the PASE data were available only starting 2 years after enrollment, all participants in this study had early PD. This disease characteristic may explain the lack of difference between physical activity habits among PD and HC participants. Prior studies have demonstrated lower levels of physical activity in moderate PD compared to controls [11,21]. Our data demonstrate decline in physical activity levels over time in the PD group, which suggests that, with additional follow up, significant differences between PD and HC may emerge. Prior smaller studies have also demonstrated decline in activity levels over time in PD patients [10,22]. While there was no significant change over time in any particular PASE subscore, there was a trend toward a decline in the work subscore. This may suggest that some of the decline in PASE over time could be due to change in employment status or levels of physical activity at work. Although reverse causation (i.e. reduced levels of exercise due to underlying disease severity or progression) cannot be ruled out by the current study, the lack of difference between physical activity levels among early PD and HC suggests that lower levels of physical activity are not a disease characteristic of PD per se, but that the disease progression and accumulation of disability may lead to reduction in activity levels.

One of the most compelling outcomes is the association of baseline (year 2) levels of physical activity with the rates of disease progression longitudinally over 2 years of follow up (years 2–4), with higher levels of physical activity being associated with less progression of motor symptoms, activities of daily living, depression and anxiety, cognitive decline and, after controlling for motor symptoms, sleep quality. These

Table 4
Impact of baseline (year 2) PASE score on the Rate of Progression of Disability Over Years 2–4 in PD (Adjusting for MDS-UPDRS Part III Score).

Variable	# Subjects	Estimate	Univariate
	Missing	Value (95% CI)	p-value
MDS-UPDRS Total Score	79	−0.0063 (−0.0118, −0.0007)	**0.027**
MDS-UPDRS Part I	79	−0.0029 (−0.0067, 0.0008)	0.122
MDS-UPDRS Part II	79	−0.0036 (−0.0068, −0.0005)	**0.023**
MDS-UPDRS Part IV	79	0.0003 (−0.0015, 0.0022)	0.716
MDS-UPDRS Walking and Balance	80	−0.0020 (−0.0039, −0.0001)	**0.038**
TD Score	79	−0.0000 (−0.0003, 0.0002)	0.746
PIGD score	79	−0.0003 (−0.0005, −0.0000)	**0.032**
Postural Instability	127	−0.0006 (−0.0059, 0.0047)	0.824
Modified Schwab & England ADL	79	0.0130 (0.0064, 0.0195)	**0.0001**
MOCA	79	*	*
HVLT Total Score	79	0.0046 (−0.0025, 0.0117)	0.202
Benton Judgement of Line Orientation	79	0.0008 (−0.0011, 0.0026)	0.404
Semantic Fluency	79	*	*
Letter Number Sequencing	79	−0.0003 (−0.0027, 0.0022)	0.831
Symbol Digit Modalities	79	0.0103 (0.0029, 0.0178)	**0.007**
MDS-UPDRS Part I Sleep	79	*	*
MDS-UPDRS Part I Fatigue	79	−0.0011 (−0.0028, 0.0006)	0.189
Epworth Sleepiness Scale Score	79	−0.0008 (−0.0038, 0.0021)	0.573
REM Sleep Behavior Disorder	79	0.0001 (−0.0015, 0.0017)	0.924
SCOPA-AUT Total Score	79	0.0007 (−0.0047, 0.0060)	0.805
GDS	79	−0.0029 (−0.0050, −0.0008)	**0.007**
State-Trait Anxiety Index	79	−0.0205 (−0.0328, −0.0082)	**0.001**
Contralateral Caudate	79	0.0003 (−0.0003, 0.0008)	0.372
Ipsilateral Caudate	79	0.0004 (−0.0004, 0.0011)	0.334
Contralateral Putamen	79	−0.0000 (−0.0003, 0.0002)	0.852
Ipsilateral Putamen	79	−0.0001 (−0.0005, 0.0004)	0.753
LED	79	0.0856 (−0.2179, 0.3891)	0.580
PASE Score by Time Interaction Effects			
MOCA			**0.022****
Year 2 to Year 3	79	−0.0022 (−0.0067, 0.0022)	0.327**
Year 2 to Year 4	79	0.0025 (−0.0011, 0.0062)	0.170**
Semantic Fluency			**0.047****
Year 2 to Year 3	79	−0.0032 (−0.0184, 0.0120)	0.675**
Year 2 to Year 4	79	−0.0131 (−0.0252, −0.0010)	**0.034****
MDS-UPDRS Part I Sleep			**0.048****
Year 2 to Year 3	79	−0.0029 (−0.0056, −0.0002)	**0.033****
Year 2 to Year 4	79	−0.0026 (−0.0048, −0.0004)	**0.021****

Note: If estimate = * then evidence of a significant interaction effect over time. Otherwise, not enough evidence to support an interaction.
** p-value is for an overall PASE Score and time interaction; Analyses adjust for age, gender, disease duration, and MDS-UPDRS part III score.
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Bold values indicates: $p < 0.05$.

findings provide hope that strategies to increase physical activity and exercise could serve as potential disease-modifying interventions in patients with early PD and could therefore guide clinical care. Previous cross-sectional studies also support the notion that higher levels of physical activity are associated with less severe motor symptoms and less depression [14]. Another large observational study reported similar results. That study evaluated the impact of self-reported minutes of exercise per week on disease progression over one year in PD patients with a wide range of disease severity, finding that regular exercise at baseline was associated with better quality of life and mobility, and less decline in verbal cognitive function over 1 year [8]. Whether exercise achieves neuroprotective, neurorestorative, neuromodulatory or just compensatory effects remains to be determined.

The ability of physical activity and exercise to offer neuroprotective effects has been explored in animal models, which show that exercise reduces 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced dopamine neurotoxicity, improves neurotrophic factor signaling, and reduces mitochondrial dysfunction, oxidative stress, and neuroinflammation in animal models of PD [23–26]. Further, in epidemiological studies, people with higher physical activity levels also have lower risk for later development of PD [4–7]. In one study, higher physical activity was associated with lower PD risk only in men, while in other studies, the effect was present for men and women [4–7]. There was also an influence of the intensity of physical activity and the age at which people were active [4–7]. As is the case with most human studies, we cannot definitively determine if this association is causative or correlative, making it difficult to say with certainty that exercise is neuroprotective. This is further confounded by the findings that exercise provides some symptomatic benefit in disease-manifest PD [2,27]. Notably, our analysis did not demonstrate an association of physical activity with the rate of change of presynaptic dopaminergic function, as measured by DaT imaging, or with the LED. A finding of increased DaT binding or reduced need for dopaminergic medications in patients with higher physical activity might have provided better evidence to suggest a neuroprotective effect, but the absence of those associations does not necessarily exclude or argue against disease modifying effects of exercise. Thus, the current study supports the idea that physical activity is beneficial in PD, but the mechanisms underlying these effects remain to be elucidated.

Another interesting finding is that physical activity in this cohort of early PD participants is associated with lower PIGD score over time. These findings are consistent with a prior cross-sectional study that showed an association of physical activity with fewer axial motor symptoms [13]. The PIGD motor phenotype has been shown to predict more rapid progression of disease severity [28] and is associated with more disabling non-motor symptoms such as psychosis and cognitive dysfunction [29]. Of note, in the current analysis we report absolute scores for tremor and PIGD but not TD/PIGD ratios as we have

previously demonstrated that PIGD subtype is unstable in early PD [30]. From the current data, we cannot definitively conclude whether those with more severe disease (higher PIGD score) are less able to participate in physical activity, or if lower activity levels lead to worse motor phenotype. Most likely, this is a bidirectional relationship. In light of the heterogeneity of PD symptoms, exercise/activity prescriptions targeted toward the physical capability of individual patients may increase activity levels across a range of disease severity. Longer follow up of the cohort will be informative in that regard.

Higher physical activity levels were also associated with less decline in some non-motor symptoms, including cognitive function, depression, anxiety, and, after adjusting for MDS-UPDRS part III, sleep quality. This is a promising finding because there are few effective pharmacological therapies proven to improve these symptoms in PD. In fact, non-pharmacologic interventions such as exercise can improve cognitive performance, sleep quality, and mood in PD [1,2,31].

Strengths of this study include the longitudinal nature of the investigation and the large cohort of well-characterized early PD and matched HC participants. Limitations include the lack of an objective measure of physical activity, relying instead on subjective patient report, which has the risk of introducing reporting bias. However, the PASE is a validated measure of physical activity that has been demonstrated to correlate with objective measures of aerobic capacity, walking speed, and activity monitoring [16,18] and the subjective nature of the reporting would be expected to affect all participants (PD and HC) equally. Nonetheless, It will be valuable to validate self-reported activity level with the data derived from wearable sensors. The findings from the current study can be used to guide design of future longitudinal studies that can employ objective measures of physical activity. Indeed, such assessments are planned for PPMI in the near future. An additional limitation of the study is the lack of correction for multiple comparisons. Despite this, the findings provide valuable information to generate hypotheses for further exploration in future studies. Another limitation is that the current study cannot detect the threshold of intensity, duration, or type of physical activity that might have the most meaningful impact on PD motor and non-motor symptoms. Therefore, additional studies with specific interventions are needed to define the ideal exercise prescription for patients with early PD.

In conclusion, this large, longitudinal, case-control study shows that levels of physical activity do not differ between early PD and matched HC, but that physical activity declines over a relatively short time in PD. Exploratory analyses further show that higher self-reported levels of physical activity are associated with less progression of motor symptoms, PIGD phenotype, activities of daily living, cognitive decline, depression, anxiety, and sleep quality. These findings emphasize the importance of encouraging physical activity in patients with PD from the time of diagnosis for improvement in both motor and non-motor symptoms. While future randomized interventional studies will be critical for providing evidence delineating the underlying biology of exercise benefits, the current study supports the idea that exercise is a readily available, cost effective and reasonably safe treatment modality that should be recommended as standard of care for all PD patients.

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Conflicts of interest

Relevant Conflicts of Interest/financial disclosures related to this work:

Dr. Amara reports no disclosures.
Dr. Chahine reports no disclosures.
Mr. Seedorff reports no disclosures.
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Appendix A. Supplementary data

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