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Tsukita, Kazuto ...[et al]. Long-term Effect of Regular Physical Activity and Exercise Habits in Patients With Early Parkinson Disease. Neurology 2022, 98(8): e859-e871

RESEARCH ARTICLE OPEN ACCESS

# Long-term Effect of Regular Physical Activity and Exercise Habits in Patients With Early Parkinson Disease

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*Neurology*® 2022;98:e859-e871. doi:10.1212/WNL.0000000000013218

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## Abstract

### Background and Objectives

Owing to the lack of long-term observations or comprehensive adjustment for confounding factors, reliable conclusions regarding long-term effects of exercise and regular physical activity in Parkinson disease (PD) have yet to be drawn. Here, using data from the Parkinson's Progression Markers Initiative study that includes longitudinal and comprehensive evaluations of many clinical parameters, we examined the long-term effects of regular physical activity and exercise habits on the course of PD.

### Methods

In this retrospective, observational cohort study, we primarily used the multivariate linear mixed-effects models to analyze the interaction effects of their regular physical activity and moderate to vigorous exercise levels, measured with the Physical Activity Scale for the Elderly questionnaire, on the progression of clinical parameters, after adjusting for age, sex, levodopa equivalent dose, and disease duration. We also calculated bootstrapping 95% confidence intervals (CIs) and conducted sensitivity analyses using the multiple imputation method and subgroup analyses using propensity score matching to match for all baseline background factors.

### Results

Two hundred thirty-seven patients with early PD (median [interquartile range] age, 63.0 [56.0–70.0] years, male 69.2%, follow-up duration 5.0 [4.0–6.0] years) were included. Regular physical activity and moderate to vigorous exercise levels at baseline did not significantly affect the subsequent clinical progression of PD. However, average regular overall physical activity levels over time were significantly associated with slower deterioration of postural and gait stability (standardized fixed-effects coefficients of the interaction term [$\beta_{\text{interaction}}$] = −0.10 [95% CI −0.14 to −0.06]), activities of daily living ($\beta_{\text{interaction}}$ = 0.08 [95% CI 0.04–0.12]), and processing speed ($\beta_{\text{interaction}}$ = 0.05 [95% CI 0.03–0.08]) in patients with PD. Moderate to vigorous exercise levels were preferentially associated with slower decline of postural and gait stability ($\beta_{\text{interaction}}$ = −0.09 [95% CI −0.13 to −0.05]), and work-related activity levels were primarily associated with slower deterioration of processing speed ($\beta_{\text{interaction}}$ = 0.07 [95% CI 0.04–0.09]). Multiple imputation and propensity score matching confirmed the robustness of our results.

### Discussion

In the long term, the maintenance of high regular physical activity levels and exercise habits was robustly associated with better clinical course of PD, with each type of physical activity having different effects.

### Trial Registration Information

ClinicalTrials.gov Identifier: NCT01176565.

### Classification of Evidence

This study provides Class II evidence that sustained increase in overall regular physical activity levels in patients with early PD was associated with slower decline of several clinical parameters.

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The Article Processing Charge was funded by the authors.

## Glossary

**AAN** = American Academy of Neurology; **app** = application; **CI** = confidence interval; **HC** = healthy control; **LEDD** = levodopa equivalent daily dose; **MDS-UPDRS** = Movement Disorders Society–sponsored revision of the Unified Parkinson's Disease Rating Scale; **MSE-ADL** = Modified Schwab & England Activity of Daily Living; **PASE** = Physical Activity Scale for the Elderly; **PD** = Parkinson disease; **PIGD** = Postural Instability and Gait Disturbance; **PPMI** = Parkinson's Progression Markers Initiative; **SDMT** = Symbol Digit Modalities Test.

Parkinson disease (PD), in which abnormal α-synuclein aggregates play a key pathologic role, is the second most common neurodegenerative disease after Alzheimer disease.[1,2] Furthermore, PD was the fastest-increasing neurologic disease between 1990 and 2017, with the aging of the population contributing to much of that increase.[3] Clinically, PD is characterized by the gradual worsening of various motor and nonmotor symptoms.[1,2] Medications such as levodopa are effective in alleviating the motor symptoms of PD, especially in the early stages of the disease; however, as the disease progresses, medication-resistant symptoms such as postural instability and cognitive impairment become apparent, causing medical treatment to become more challenging.[4-6] Therefore, one of the biggest frustrations for both patients with PD and clinicians is that there is still no disease-modifying treatment to slow the progression of disease.[7]

Exercise has long been postulated as a promising intervention that can modify the long-term clinical course of patients with PD.[8,9] Recently, 2 rigorously designed randomized clinical trials have confirmed that aerobic exercise can improve global motor function at least during the intervention period, especially when high-intensity exercise is involved.[10,11] It is also generally accepted by other randomized clinical trials that interventions with balance, gait, Tai chi, and dance training can improve balance and gait performance.[12] However, in most of these studies, the assessment was conducted solely during the intervention period, and the interventional period was short (<6 months).[12] Recent observational studies have suggested that exercise habits at baseline were associated with slower disease progression over several years. However, these observational studies may not have been well adjusted for confounding factors partly due to the lack of comprehensive assessments of clinical symptoms; therefore, their results may merely reflect differences in disease traits.[13,14]

In addition to exercise (i.e., structured, repetitive, and purposive activities that aim to improve components of physical fitness), there were some promising results regarding the effect of regular physical activity (i.e., daily life activities involving any bodily movement that demands energy expenditure) on the disease course of PD. Previous observational studies have shown that not only exercise habits but also overall regular physical levels at baseline are associated with slower motor and cognitive decline over a few years.[14-17] However, again, the short follow-up period and the lack of sufficient adjustment of confounding factors remain important issues. Therefore, no reliable conclusions have yet been drawn regarding the long-term disease-modifying effects of exercise and high daily physical activity levels in patients with PD.

The Parkinson's Progression Markers Initiative (PPMI) is a large international multicenter study (ClincalTrials.gov NCT01141023) that has been underway since 2012; it aims to gain greater understanding of the disease course of PD and to identify disease modifiers.[18] The PPMI study includes longitudinal and comprehensive evaluations of background factors, motor function, and cognitive function, as well as regular physical activity levels as measured by the Physical Activity Scale for the Elderly (PASE) questionnaire, which is a widely validated self-report questionnaire designed to quantify regular physical activity levels of individuals >65 years of age.[19-21] Therefore, using the PPMI study data, we aimed to examine the long-term effects of regular physical activity and exercise habits on the disease course of PD. Specifically, using the PASE questionnaire, we quantified several domains of regular physical activities, including leisure, household, work, and exercise activities, and examined the interaction effects of these activities on the course of various functions, including motor and cognitive functions, the presence of depression, autonomic symptoms, and sleep-related symptoms.

# Methods

## Study Participants

This is a retrospective, observational cohort study using data from PPMI study, which were obtained from the PPMI database[22] on April 3, 2021. The PPMI study is an international, multicenter, observational study that began in 2012 and is still ongoing. In the original PPMI study, the following participants were prospectively enrolled and longitudinally assessed for a number of clinical parameters at predefined time points: healthy controls (HCs), patients with de novo PD who were not on dopaminergic medication and exhibited presynaptic dopaminergic terminal loss as confirmed by dopamine transporter imaging, patients who were at high probability of being in the prodromal phase of PD, and patients with parkinsonism in the absence of evidence of dopaminergic deficit on dopamine transporter imaging. Further details of the study protocol are available on the PPMI website.[23]

Among patients with PD registered in the PPMI database, the participants in this longitudinal study were selected on the basis of the following criteria. First, at least 3 sets of PASE questionnaire data should be available because the effect of regular physical activity over the subsequent 2 years was already investigated previously and our study aims to focus on more longer-term effect.[16,19-21] Second, the results of the "off" score of the Movement Disorders Society–sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS) part 3 at the time when each participant first responded to the PASE questionnaire should also be available because it would be very difficult to assess changes in motor function over time without them. To better understand the clinical characteristics of the patients with PD who participated in our study, we also included HCs with the same inclusion criteria only for the comparison of clinical parameters.

In the original PPMI study, the results of the PASE questionnaire were first collected in the second year after the original enrollment of patients with de novo PD and annually afterward.[16] Baseline in this study was defined as the point at which the results of the PASE questionnaire were first collected; therefore, the definition of baseline was different from that used in the original PPMI study. In the data downloaded on April 3, 2021, the median follow-up duration from the baseline of our study was 5 years (interquartile range 4–6 years); therefore, we used the annual follow-up results of the PASE questionnaire over a period of up to 6 years.

## Standard Protocol Approvals, Registrations, and Patient Consents

Each PPMI participating site received approval from the local ethics committee before study initiation, and written informed consent was obtained from all participants before participation. Our study strictly adheres to the publication policy in the PPMI study,[24] and we have obtained permission for publishing our research by the Data & Publication Committee of the PPMI study.

## Physical Activity

Regular physical activity levels were quantified with the PASE questionnaire.[19,20] The PASE questionnaire is a widely validated 12-item self-report questionnaire that uses the intensity, frequency, and duration of physical activity over the prior week to calculate the total PASE score, which ranges from 0 to 793, with higher scores indicating higher physical activity.[19-21] The PASE score has a significant correlation with the objective measures of physical activity.[19-21] The score combines information on leisure-, household-, and work-related activities; therefore, in addition to quantifying the overall regular physical activity through the total PASE score, the PASE questionnaire can be used to quantify each domain of physical activity via the PASE leisure, PASE household, and PASE work scores.[19-21] Quality metrics recently published by the American Academy of Neurology (AAN) recommend that regular exercise for patients with PD should consist of at least 150 minutes of moderate-intensity activity per week.[25] Therefore, as a measure of exercise habit, we also quantified moderate to vigorous exercise levels using the sum of the scores from question 4, which quantified moderate sports and recreational activities in the past week, and question 5, which quantified intense sports and recreational activities in the past week, as well as the percentage of participants who met the recommendations of AAN quality metrics.

## Clinical Evaluations

In addition to age, sex, disease duration (time since the onset of symptoms), and Hoehn-Yahr stage, we extracted the baseline and annual follow-up data pertaining to motor and cognitive function, the presence of depression, autonomic symptoms, sleep-related symptoms, and levodopa equivalent daily dose (LEDD). We assessed the global motor function in the "off" state using the MDS-UPDRS part 3 score.[26] In the PPMI study, the "off" state was defined as the state that occurred after the patients had withheld their dopaminergic medication for at least 12 hours. To further evaluate specific motor functions, we also calculated the Postural Instability and Gait Disturbance (PIGD) and tremor subscores.[27]

We assessed global cognitive function using the Montreal Cognitive Assessment.[28] To assess the subdomains of cognitive function, we used the delayed recall T score of the Hopkins Verbal Learning Test–Revised as a measure of verbal recent memory,[29] total score of the Letter-Number Sequencing test as a measure of working memory,[30] and total score of the Symbol Digit Modalities Test (SDMT) as a measure of processing speed.[31]

Furthermore, we used the total score of the 15-item Geriatric Depression Scale as a measure of depression,[32] total score of the Scales for Outcomes in Parkinson's Disease–Autonomic Dysfunction as a measure of autonomic symptoms,[33] total score of the Epworth Sleepiness Scale as a measure of daytime sleepiness,[34] total score of the REM Sleep Behavior Disorder Screening Questionnaire as a measure of dream-enacting behavior,[35] and Modified Schwab & England Activity of Daily Living (MSE-ADL) scale as a measure for ADL.[36] For LEDD calculation, the LEDD of each drug was calculated by multiplying its daily dose by its conversion factor,[37] and total LEDD at a particular time point was then calculated by adding the LEDD of all the drugs. Further details on the collection of these data can be obtained from the PPMI website.[23]

## Statistical Analyses

The first author (K.T.), who is certified by the Japan Statistical Society (grade2), primarily conducted statistical analyses using self-made R scripts for the statistical software R (version 4.0.5, R Foundation for Statistical Computing, Vienna, Austria). We performed the Wilcoxon rank-sum test, Pearson $\chi^2$ test, and Spearman rank correlation, as appropriate.

To adjust for covariates and to examine the interaction effect, we used the multivariate linear mixed effects model (random intercept/slope model with parameters being estimated using maximum likelihood method) with an interaction term because each participant provides several data points.[38] In our model, each clinical parameter represented a response

**Table 1** Baseline Characteristics of the Enrolled Participants

| | PD (n = 237)[a] | HCs (n = 158)[a] | *p* Value[b] |
|---|---|---|---|
| **Age, y** | 63.0 (56.0–70.0) | 64.0 (58.0–71.0) | 0.51 |
| **Female, n (%)** | 73 (30.8) | 60 (38.0) | 0.14 |
| **Disease duration, y** | 3.0 (3.0–5.0) | — | |
| **Hoehn-Yahr stage** | 2.0 (1.0–2.0) | 0.0 (0.0–0.0) | <0.001 |
| **Levodopa equivalent dose, mg** | 100.0 (0.0–300.0) | — | |
| **PASE leisure score** | 49.0 (17.8–92.6) | 53.0 (22.7–105.4) | 0.36 |
| **PASE household score** | 86.0 (50.0–121.0) | 86.0 (61.0–121.0) | 0.24 |
| **PASE work score** | 0.0 (0.0–48.0) | 0.0 (0.0–49.5) | 0.88 |
| **PASE total score** | 175.0 (110.5–250.5) | 182.2 (131.4–242.5) | 0.28 |
| **PASE score of moderate to vigorous exercise** | 0.11 (0.00–0.75) | 0.25 (0.00–0.93) | 0.38 |
| **AAN quality metrics met, n (%)** | 105 (44.3) | 71 (44.9) | 0.90 |
| **"Off" MDS-UPDRS part 3 score** | 25.0 (18.0–34.0) | 0.0 (0.0–2.0) | <0.001 |
| **"Off" MDS-UPDRS tremor subscore** | 6.0 (3.0–10.0) | 0.0 (0.0–0.0) | <0.001 |
| **"Off" MDS-UPDRS PIGD subscore** | 1.0 (1.0–2.0) | 0.0 (0.0–0.0) | <0.001 |
| **MoCA total score** | 27.0 (25.0–29.0) | 28.0 (26.0–29.0) | <0.001 |
| **HVLT-R delayed recall T score** | 45.0 (37.0–55.0) | 52.0 (42.0–58.0) | <0.001 |
| **JLO total score** | 26.0 (23.5–28.0) | 26.0 (24.0–30.0) | 0.44 |
| **Missing, n** | 1 | 0 | |
| **LNS total score** | 11.0 (9.0–12.0) | 11.0 (9.0–13.0) | 0.23 |
| **SDMT total score** | 42.0 (35.0–48.0) | 47.0 (40.0–54.0) | <0.001 |
| **Missing, n** | 0 | 1 | |
| **SCOPA-AUT total score** | 13.0 (7.0–20.0) | 7.0 (4.0–13.0) | <0.001 |
| **Missing, n** | 1 | 0 | |
| **GDS-15 total score** | 5.0 (5.0–6.0) | 5.0 (5.0–5.0) | 0.024 |
| **Missing, n** | 1 | 0 | |
| **ESS total score** | 6.0 (4.0–9.0) | 5.0 (3.0–7.0) | 0.015 |
| **RBDSQ total score** | 5.0 (3.0–7.0) | 3.0 (2.0–5.0) | <0.001 |
| **MSE-ADL score** | 90.0 (85.0–95.0) | 100.0 (100.0–100.0) | <0.001 |
| **Missing, n** | 1 | 145 | |

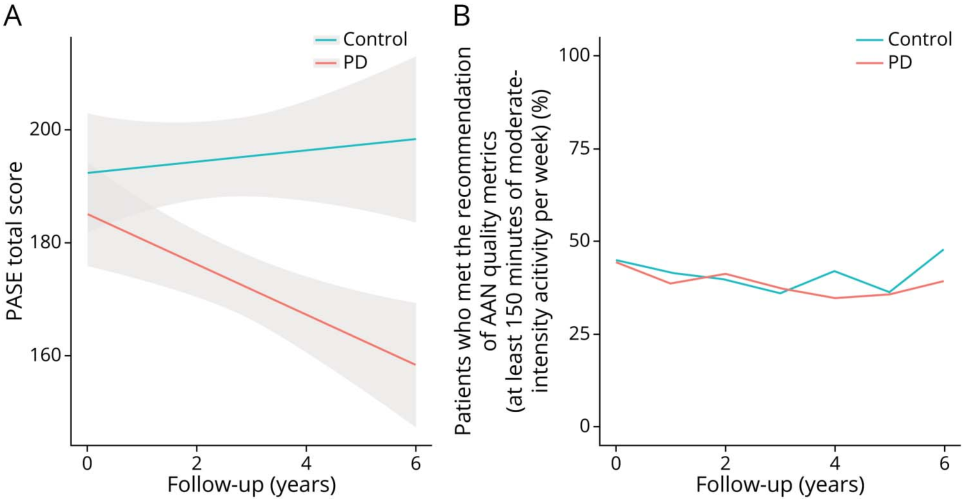
Abbreviations: AAN = American Academy of Neurology; ESS = Epworth Sleepiness Scale; GDS-15 = 15-item version of Geriatric Depression Scale; HC= healthy control; HVLT-R = Hopkins Verbal Learning Test–Revised; JLO = Judgment of Line Orientation; LNS = Letter-Number Sequencing; MDS-UPDRS = Movement Disorders Society–sponsored revision of the Unified Parkinson's Disease Rating Scale; MoCA = Montreal Cognitive Assessment; MSE-ADL = Modified Schwab & England Activities of Daily Living scale; PASE = Physical Activity Scale for Elderly; PD = Parkinson disease; PIGD = Postural Instability and Gait Disturbance; RBDSQ = REM sleep Behavior Disorder Screening Questionnaire; SCOPA-AUT = Scales for Outcomes in Parkinson's Disease–Autonomic Dysfunction; SDMT = Symbol Digit Modalities Test.

[a] Data are expressed as median (interquartile range) or number (percentage).

[b] The *p* values were obtained by Wilcoxon rank-sum test or Pearson $\chi^2$ test, as appropriate. Because these *p* values were not adjusted for multiple comparisons and there were 24 comparison items, the value of 0.05 divided by 24 was used to determine statistical significance.

variable, while predictor variables with fixed effects consisted of the duration of follow-up from the baseline, each score calculated from the PASE questionnaire (PASE total score, PASE leisure score, PASE household score, PASE work score, or moderate to vigorous exercise score, as described above), age, LEDD, disease duration, sex, an interaction effect term between the first 2 predictor variables, and a predictor variable with random effects was each participant identification number. To make the result more interpretable by putting different variables on the same scale and to obtain

**Figure 1** Temporal Changes in Overall Regular Physical Activity Levels and Proportion of Participants With Appropriate Exercise Habits



Linear regression lines showing temporal changes in overall regular physical activity levels quantified by the total score of the Physical Activity Scale for the Elderly (PASE) questionnaire (A) and line graphs showing temporal changes in the percentage of participants meeting the recommendation from quality metrics published by the American Academy of Neurology (AAN) (B). Note that in the control group, the PASE total score appears to have an increasing trend over time, but this trend did not reach statistical significance. Gray areas represent the 95% confidence intervals of the regression lines. PD = Parkinson disease.

standardized fix-effects coefficients (β), all continuous variables were $z$ transformed in advance by subtracting the mean and dividing by the SD. We primarily used the likelihood ratio test as a means to obtain $p$ value in assessing the effect of adding the interaction term into a multivariate linear mixed-effects model.[38] Although this model is very robust even against violations of the assumption that, for example, the residuals of the model should be normally distributed and can also handle missing data,[39] we confirmed the robustness of our result by computing 95% confidence intervals (CIs) for each $\beta_{\text{interaction}}$ estimate using the bootstrapping method (1,000 times) and conducting sensitivity analyses using the multiple imputation for missing data with expectation-maximization with bootstrapping algorithm (repeated 100 times to compute 95% CIs).

Furthermore, we subsequently conducted subgroup analyses using propensity score matching to visualize and confirm the results. For this purpose, after we dichotomized patients with PD into lower and higher regular physical activity groups using the median or 75th percentile level of regular physical activity, propensity score matching was performed to obtain 2 groups that were matched for all baseline background factors other than regular physical activity levels. After a caliper width was set to 0.25 of the SD of the logit of the propensity score, 1-to-1 matching using the nearest-neighbor method without replacement was performed.[40,41] The balance of covariates between 2 propensity score–matched groups was evaluated by standardized mean differences.[42]

We considered a value of $p < 0.05$ to be statistically significant, and in the case of multiple comparisons, we considered a Bonferroni-corrected value of $p$, which is calculated by multiplying original $p$ value by the number of comparisons, of <0.05 to be statistically significant. Values are presented as median (interquartile range) or with a 95% CI.

## Data Availability

All data used in this study are available in the PPMI database.[22] The R scripts used in this study are deposited in Dryad (doi.org/10.5061/dryad.hqbzkh1gm).

## Classification of Evidence

This study provides Class II evidence that sustained increase in overall regular physical activity levels in patients with early PD was associated with slower decline of several clinical parameters.

# Results

## Clinical Characteristics of Patients With PD

At the baseline, we ultimately included 237 patients with PD (Table 1). The flowchart in eFigure 1 (links.lww.com/WNL/B703) shows the number of patients with PD at each stage of the patient inclusion process in our study.

At the baseline, compared to 158 HCs with the same inclusion criteria, patients with PD showed significantly greater impairment in motor, cognitive, and autonomic functions. However, regular physical activity levels and moderate to vigorous exercise levels were not significantly different between the 2 groups (Table 1).

During the follow-up period, overall regular physical activity level of patients with PD gradually decreased with the PASE total score decreasing by 4.5 points per year (95% CI −7.3 to −1.7; Spearman $\rho = -0.08$ [95% CI −0.14 to −0.03], $p < 0.01$), while no significant change was observed longitudinally in HCs (Spearman $\rho = 0.04$ [95% CI −0.03 to −0.11], $p = 0.26$) (Figure 1A). Moderate to vigorous exercise levels showed a decreasing trend in both patients with PD and HCs, but this trend did not reach statistical

**Table 2** Temporal Change in Clinical Parameters of Patients With PD

| | Follow-up year | | | | | |
|---|---|---|---|---|---|---|
| | **1 (n = 223)**[a] | **2 (n = 226)**[a] | **3 (n = 209)**[a] | **4 (n = 191)**[a] | **5 (n = 153)**[a] | **6 (n = 118)**[a] |
| **Age, y** | 64.0 (57.0–71.0) | 65.0 (58.0–72.8) | 66.0 (59.0–73.0) | 67.0 (59.5–74.0) | 68.0 (61.0–74.0) | 69.0 (62.0–75.0) |
| **Female, n (%)** | 71 (31.8) | 73 (32.3) | 65 (31.1) | 56 (29.3) | 46 (30.1) | 33 (28.0) |
| **Disease duration, y** | 4.0 (3.5–6.0) | 5.0 (5.0–6.0) | 6.0 (5.0–7.0) | 7.0 (6.0–9.0) | 8.0 (7.0–9.0) | 9.0 (8.0–10.0) |
| **Hoehn-Yahr stage** | 2.0 (2.0–2.0) | 2.0 (2.0–2.0) | 2.0 (2.0–2.0) | 2.0 (2.0–2.0) | 2.0 (2.0–2.0) | 2.0 (2.0–2.0) |
| **Missing, n** | 20 | 34 | 29 | 26 | 19 | 15 |
| **Levodopa equivalent dose, mg** | 200.0 (100.0–400.0) | 300.0 (100.0–450.0) | 300.0 (140.0–600.0) | 333.0 (160.0–625.0) | 300.0 (150.0–700.0) | 400.0 (199.6–701.3) |
| **PASE leisure score** | 48.1 (22.6–78.1) | 52.9 (17.8–87.3) | 52.9 (17.6–91.6) | 42.8 (17.6–105.4) | 45.5 (17.8–77.6) | 47.4 (17.6–79.2) |
| **PASE household score** | 85.0 (50.0–115.5) | 85.0 (50.0–116.0) | 85.0 (50.0–116.0) | 85.0 (50.0–115.0) | 80.0 (50.0–116.0) | 80.0 (50.0–106.0) |
| **PASE work score** | 0.0 (0.0–27.0) | 0.0 (0.0–12.0) | 0.0 (0.0–9.0) | 0.0 (0.0–12.0) | 0.0 (0.0–0.0) | 0.0 (0.0–0.0) |
| **PASE total score** | 159.9 (106.4–235.0) | 158.2 (106.7–232.0) | 154.1 (102.6–227.1) | 156.3 (103.6–233.2) | 142.2 (87.4–205.9) | 148.7 (87.6–201.5) |
| **PASE score of moderate to vigorous exercise** | 0.1 (0.0–0.8) | 0.1 (0.0–0.8) | 0.1 (0.0–0.8) | 0.1 (0.0–0.8) | 0.0 (0.0–0.8) | 0.1 (0.0–0.6) |
| **AAN quality metrics met, n (%)** | 86 (38.6) | 93 (41.2) | 78 (37.3) | 75 (39.3) | 53 (34.6) | 42 (35.6) |
| **"Off" MDS-UPDRS part 3 score** | 26.0 (20.0–35.0) | 31.0 (22.0–38.0) | 32.0 (23.0–40.0) | 33.0 (27.0–42.0) | 34.5 (23.2–45.0) | 38.0 (27.2–49.0) |
| **Missing, n** | 20 | 35 | 29 | 26 | 19 | 16 |
| **"Off" MDS-UPDRS tremor subscore** | 6.0 (3.0–10.0) | 8.0 (4.0–11.0) | 7.0 (3.0–10.0) | 7.0 (3.0–11.0) | 7.5 (3.0–11.0) | 7.0 (4.5–13.5) |
| **Missing, n** | 20 | 34 | 28 | 26 | 19 | 15 |
| **"Off" MDS-UPDRS PIGD subscore** | 2.0 (1.0–2.0) | 2.0 (1.0–2.0) | 2.0 (1.0–3.0) | 2.0 (1.0–4.0) | 2.0 (2.0–4.8) | 3.0 (2.0–5.0) |
| **Missing, n** | 20 | 35 | 29 | 26 | 19 | 16 |
| **MoCA total score** | 27.0 (25.0–29.0) | 27.0 (25.0–29.0) | 27.0 (25.0–29.0) | 27.0 (25.0–29.0) | 27.0 (25.0–29.0) | 27.0 (25.0–29.0) |
| **Missing, n** | 3 | 2 | 1 | 3 | 3 | 1 |
| **HVLT-R delayed recall T score** | 46.0 (38.0–55.0) | 50.0 (39.0–56.0) | 51.0 (40.0–59.0) | 50.0 (37.0–56.0) | 48.0 (37.0–56.0) | 45.0 (35.0–55.0) |
| **Missing, n** | 1 | 1 | 2 | 2 | 2 | 2 |
| **JLO total score** | 28.0 (24.0–28.0) | 26.0 (24.0–30.0) | 27.0 (24.0–30.0) | 26.0 (24.0–28.0) | 26.0 (22.0–28.0) | 26.0 (22.0–28.0) |
| **Missing, n** | 1 | 4 | 5 | 4 | 3 | 3 |
| **LNS total score** | 10.0 (9.0–12.0) | 10.0 (9.0–12.0) | 10.0 (8.0–12.0) | 10.0 (8.0–12.0) | 10.0 (8.0–11.5) | 10.0 (8.0–12.0) |
| **Missing, n** | 0 | 1 | 1 | 2 | 2 | 2 |
| **SDMT total score** | 41.0 (35.0–48.0) | 42.0 (33.0–49.0) | 41.0 (33.0–47.0) | 41.0 (33.8–48.0) | 38.5 (30.2–46.8) | 38.0 (28.8–45.0) |
| **Missing, n** | 1 | 2 | 0 | 3 | 3 | 2 |
| **SCOPA-AUT total score** | 14.0 (8.0–20.0) | 14.0 (9.0–22.8) | 13.0 (8.0–22.0) | 16.0 (10.0–23.8) | 18.0 (11.0–26.0) | 18.0 (13.0–26.0) |
| **Missing, n** | 0 | 0 | 0 | 1 | 0 | 1 |
| **GDS-15 total score** | 5.0 (5.0–6.0) | 5.0 (5.0–6.0) | 5.0 (5.0–6.0) | 5.0 (5.0–7.0) | 5.0 (5.0–7.0) | 5.0 (5.0–7.0) |
| **Missing, n** | 0 | 0 | 0 | 0 | 0 | 0 |
| **ESS total score** | 6.0 (4.0–9.0) | 6.0 (4.0–10.0) | 6.0 (4.0–11.0) | 6.0 (4.0–10.5) | 7.0 (4.0–11.0) | 7.0 (5.0–10.8) |
| **Missing, n** | 3 | 0 | 0 | 0 | 0 | 0 |
| **RBDSQ total score** | 5.0 (3.0–8.0) | 5.0 (3.0–8.0) | 5.0 (3.0–8.0) | 6.0 (4.0–9.0) | 7.0 (4.0–9.0) | 7.0 (4.0–10.0) |
| **Missing, n** | 0 | 2 | 0 | 1 | 0 | 0 |

Continued

**Table 2** Temporal Change in Clinical Parameters of Patients With PD *(continued)*

| | Follow-up year | | | | | |
|---|---|---|---|---|---|---|
| | **1 (n = 223)$^a$** | **2 (n = 226)$^a$** | **3 (n = 209)$^a$** | **4 (n = 191)$^a$** | **5 (n = 153)$^a$** | **6 (n = 118)$^a$** |
| **MSE-ADL score** | 90.0 (80.0–90.0) | 90.0 (80.0–90.0) | 90.0 (80.0–90.0) | 90.0 (80.0–90.0) | 80.0 (80.0–90.0) | 80.0 (80.0–90.0) |
| **Missing, n** | 0 | 1 | 0 | 2 | 0 | 0 |

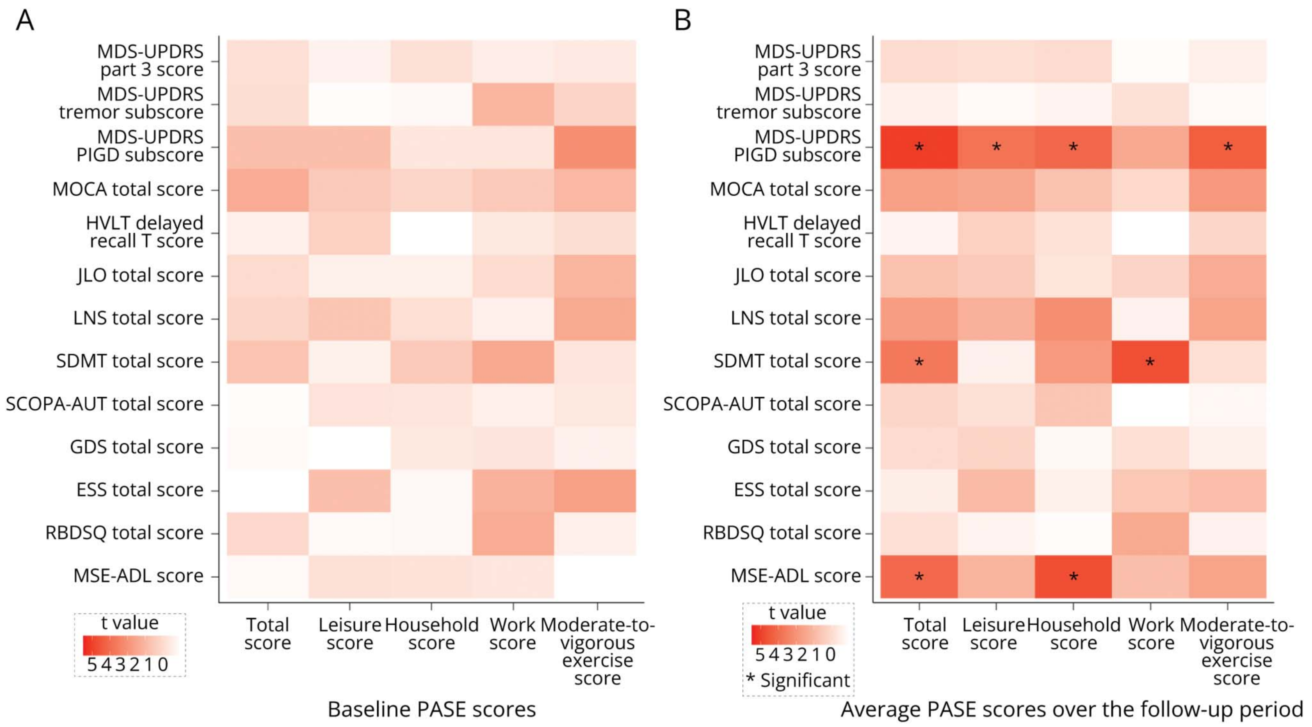
Abbreviations: AAN = American Academy of Neurology; ESS = Epworth Sleepiness Scale; GDS-15 = 15-item version of Geriatric Depression Scale; HVLT-R = Hopkins Verbal Learning Test–Revised; JLO = Judgment of Line Orientation; LNS = Letter-Number Sequencing; MDS-UPDRS = Movement Disorders Society–sponsored revision of the Unified Parkinson's Disease Rating Scale; MoCA = Montreal Cognitive Assessment; MSE-ADL = Modified Schwab & England Activities of Daily Living scale; PASE = Physical Activity Scale for Elderly; PD = Parkinson disease; PIGD = Postural Instability and Gait Disturbance; RBDSQ = REM sleep Behavior Disorder Screening Questionnaire; SCOPA-AUT = Scales for Outcomes in Parkinson's Disease–Autonomic Dysfunction; SDMT = Symbol Digit Modalities Test.

[a] Data are expressed as median (interquartile range) or number (percentage).

significance (PD: Spearman ρ = −0.04 [95% CI −0.09 to 0.02], *p* = 0.17; HCs: Spearman ρ = −0.04 [95% CI −0.11 to 0.04], *p* = 0.34). The change over time in percentage of participants who met AAN quality metrics for regular exercise regimen also did not reach statistical significance (PD: 44.3% [baseline] vs 35.6% [after 6 years], *p* = 0.12; : 44.9% [baseline] vs 47.8% [after 6 years], *p* = 0.73) (Figure 1B).

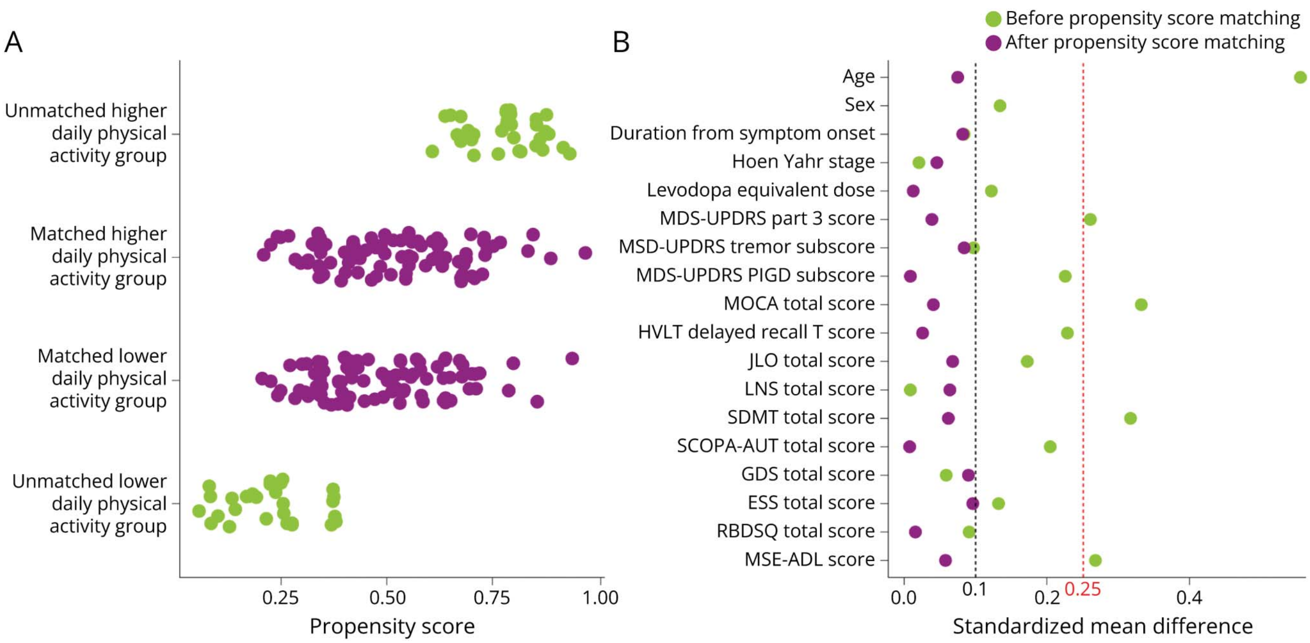
The temporal changes in all clinical variables of patients with PD are summarized in Table 2. The number of patients with PD was 223 at the 1-year follow-up, 226 at the 2-year follow-up, 209 at the 3-year follow-up, 191 at the 4-year follow-up, 153 at the 5-year follow-up, and 118 at the 6-year follow-up. Because the original PPMI study is still ongoing and the current data were downloaded on April 2021, the decline in the number of patients with PD over time in this study should

**Figure 2** Summary of the Interaction Effect of Each Regular Physical Activity Level on the Decline of Each Function in Patients With PD



Heatmaps showing the degree of interaction effect of the overall level of regular physical activity and level of different types of physical activity on the progression of each clinical parameter, as determined from the *t* value of the fixed-effects interaction term in our multivariate linear mixed-effects model. Note that there were no statistically significant interaction effects between the baseline regular physical activity levels and progression of any clinical parameters (A). However, the average regular physical activity levels over the follow-up period had statistically significant interaction effects on the temporal progression of several clinical parameters (B). ESS = Epworth Sleepiness Scale; GDS = Geriatric Depression Scale; HVLT = Hopkins Verbal Learning Test; JLO = Judgment of Line Orientation; LNS = Letter-Number Sequencing; MDS-UPDRS = Movement Disorders Society–sponsored revision of the Unified Parkinson's disease rating scale; MOCA = Montreal Cognitive Assessment; MSE-ADL = Modified Schwab & England Activities of Daily Living scale PASE = Physical Activity Scale for Elderly; PD = Parkinson disease; PIGD = Postural Instability and Gait Disturbance; RBDSQ = REM Sleep Behavior Disorder Screening Questionnaire; SCOPA-AUT = Scales for Outcomes in Parkinson's Disease–Autonomic Dysfunction; SDMT = Symbol Digit Modalities Test. *Significant association after the Bonferroni correction (Bonferroni-corrected *p* < 0.05).

**Figure 3** Distribution of Propensity Scores and Balance Measures After Propensity Score Matching



At first, patients with Parkinson disease (PD) were dichotomized according to the median of the average Physical Activity Scale for the Elderly (PASE) total score. After propensity score matching, both the higher and lower regular physical activity groups consisted of 86 patients with PD (A) and were matched such that standardized mean differences between all background factors fell within a strict cutoff of 0.1 (B). ESS = Epworth Sleepiness Scale; GDS = Geriatric Depression Scale; HVLT = Hopkins Verbal Learning Test; JLO = Judgment of Line Orientation; LNS = Letter-Number Sequencing; MDS-UPDRS = Movement Disorders Society–sponsored revision of the Unified Parkinson's disease rating scale; MOCA = Montreal Cognitive Assessment; MSE-ADL = Modified Schwab & England Activities of Daily Living scale; PIGD = Postural Instability and Gait Disturbance; RBDSQ = REM Sleep Behavior Disorder Screening Questionnaire; SCOPA-AUT = Scales for Outcomes in Parkinson's Disease–Autonomic Dysfunction; SDMT = Symbol Digit Modalities Test.

be attributed mainly to differences in baseline dates rather than differences in the background characteristics (baseline dates, July 31, 2013 [May 31, 2013–November 30, 2013] [follow up for 6 years], vs June 30, 2014 [February 28, 2014–December 16, 2014] [follow-up for ≤5 years], Bonferroni-corrected $p < 0.01$) (eTable 1, links.lww.com/WNL/B703).

## Interaction Effects of Regular Physical Activity and Moderate to Vigorous Exercise Levels on Progression of Clinical Parameters in Patients With PD

Next, using a multivariate linear mixed-effects model with an interaction term that adjusted for age, LEDD, disease duration, and sex, we analyzed whether overall regular physical activity levels and moderate to vigorous exercise levels, as well as leisure-, household-, and work-related activity levels at baseline, can alter the progression of each clinical parameter. However, no statistically significant interaction effects were found between them (Figure 2A).

We then analyzed the associations between clinical progression and the average regular physical activity levels during the follow-up period. Subsequently, we found that the average level of overall regular physical activity over the years had significant interaction effects on the PIGD subscore, MSE-ADL score, and SDMT score (PIGD subscore: β of the interaction term [$\beta_{\text{interaction}}$] = −0.10 [bootstrap 95% CI −0.14 to −0.06], $t = -5.0$, Bonferroni-corrected $p < 0.01$; MSE-ADL score: $\beta_{\text{interaction}} = 0.08$ [bootstrap 95% CI 0.04–0.12], $t = 4.1$, Bonferroni-corrected $p < 0.01$; SDMT score: $\beta_{\text{interaction}} = 0.05$ [bootstrap 95% CI 0.03–0.08], $t = 3.7$, Bonferroni-corrected $p < 0.01$) (Figure 2B and eTable 2, links.lww.com/WNL/B703). Furthermore, we found that different types of activities had different impacts on the progression of clinical parameters. Specifically, moderate to vigorous exercise levels had a preferential interaction effect on the increase in the PIGD subscore over time ($\beta_{\text{interaction}} = -0.09$ [bootstrap 95% CI −0.13 to −0.05], $t = -4.4$, Bonferroni-corrected $p < 0.01$), and the interaction effect of moderate to vigorous exercise levels was greater than the interaction effects of household-, work-, and overall leisure-related activities (Figure 2B and eTable 2). Work-related activity levels, on the other hand, had an interaction effect primarily on the progression of processing speed decline ($\beta_{\text{interaction}} = 0.07$ [bootstrap 95% CI 0.04–0.09], $t = 4.7$, Bonferroni-corrected $p < 0.01$), and the largest interaction effect of housework-related activities was seen on the deterioration of ADL ($\beta_{\text{interaction}} = 0.09$ [bootstrap 95% CI 0.05–0.12], $t = 4.7$, Bonferroni-corrected $p < 0.01$) (Figure 2B and eTable 2). Furthermore, in addition to the bootstrap 95% CIs described above, sensitivity analyses using the multiple imputation method for missing data confirmed the robustness of our model (eTable 2).

**Table 3** Baseline Clinical Characteristics of Propensity Score–matched Groups of Patients With PD

| | Lower average overall regular physical activity (n = 86)[a] | Higher average overall regular physical activity (n = 86)[a] | *p* Value[b] | SMD |
|---|---|---|---|---|
| **Age, y** | 64.5 (59.2–70.0) | 63.0 (57.0–70.0) | 0.59 | 0.075 |
| **Female, n (%)** | 26.0 (30.2) | 26.0 (30.2) | >0.99 | <0.001 |
| **Disease duration, y** | 3.5 (3.0–4.8) | 3.0 (2.2–5.0) | 0.92 | 0.082 |
| **Hoen Yahr stage** | 2.0 (2.0–2.0) | 2.0 (1.0–2.0) | 0.90 | 0.046 |
| **Levodopa equivalent dose, mg** | 100.0 (0.0–300.0) | 100.0 (0.0–224.1) | 0.78 | 0.013 |
| **"Off" MDS-UPDRS part 3 score** | 27.0 (20.5–33.0) | 23.0 (18.0–36.0) | 0.43 | 0.039 |
| **"Off" MDS-UPDRS tremor subscore** | 7.5 (3.0–10.8) | 6.0 (4.0–9.0) | 0.56 | 0.084 |
| **"Off" MDS-UPDRS PIGD subscore** | 1.5 (1.0–2.0) | 1.0 (1.0–2.0) | 0.49 | 0.009 |
| **MoCA total score** | 27.0 (25.0–29.0) | 27.0 (25.0–28.0) | 0.92 | 0.041 |
| **HVLT-R delayed recall T score** | 47.0 (36.0–57.5) | 45.0 (38.0–52.8) | 0.67 | 0.026 |
| **JLO total score** | 28.0 (24.0–28.0) | 26.0 (22.0–30.0) | 0.47 | 0.068 |
| **LNS total score** | 11.0 (9.0–12.0) | 11.0 (9.0–12.8) | 0.72 | 0.064 |
| **SDMT total score** | 42.0 (36.2–48.0) | 40.5 (35.0–48.0) | 0.29 | 0.062 |
| **SCOPA-AUT total score** | 12.0 (7.2–20.0) | 13.5 (7.0–18.8) | 0.94 | 0.008 |
| **GDS-15 total score** | 5.0 (5.0–6.0) | 5.0 (5.0–6.0) | 0.75 | 0.090 |
| **ESS total score** | 6.0 (4.0–8.8) | 6.0 (3.0–7.0) | 0.67 | 0.096 |
| **RBDSQ total score** | 4.0 (3.0–7.8) | 5.0 (4.0–7.0) | 0.60 | 0.016 |
| **MSE-ADL score** | 90.0 (90.0–90.0) | 90.0 (85.0–95.0) | 0.52 | 0.058 |

Abbreviations: ESS = Epworth Sleepiness Scale; GDS- = 15-item version of Geriatric Depression Scale; HVLT-R = Hopkins Verbal Learning Test–Revised; JLO = Judgment of Line Orientation; LNS = Letter-Number Sequencing; MDS-UPDRS = Movement Disorders Society–sponsored revision of the Unified Parkinson's Disease Rating Scale; MoCA = Montreal Cognitive Assessment; MSE-ADL = Modified Schwab & England Activities of Daily Living scale; PD = Parkinson disease; PIGD = Postural Instability and Gait Disturbance; RBDSQ = REM sleep Behavior Disorder Screening Questionnaire; SCOPA-AUT = Scales for Outcomes in Parkinson's Disease–Autonomic Dysfunction; SDMT = Symbol Digit Modalities Test; SMD = standardized mean difference.
[a] Data are expressed as median (interquartile range) or number (percentage).
[b] The *p* values were obtained by Wilcoxon rank sum test or Pearson's $\chi^2$ test, as appropriate.
These *p* values were not adjusted for multiple comparisons.

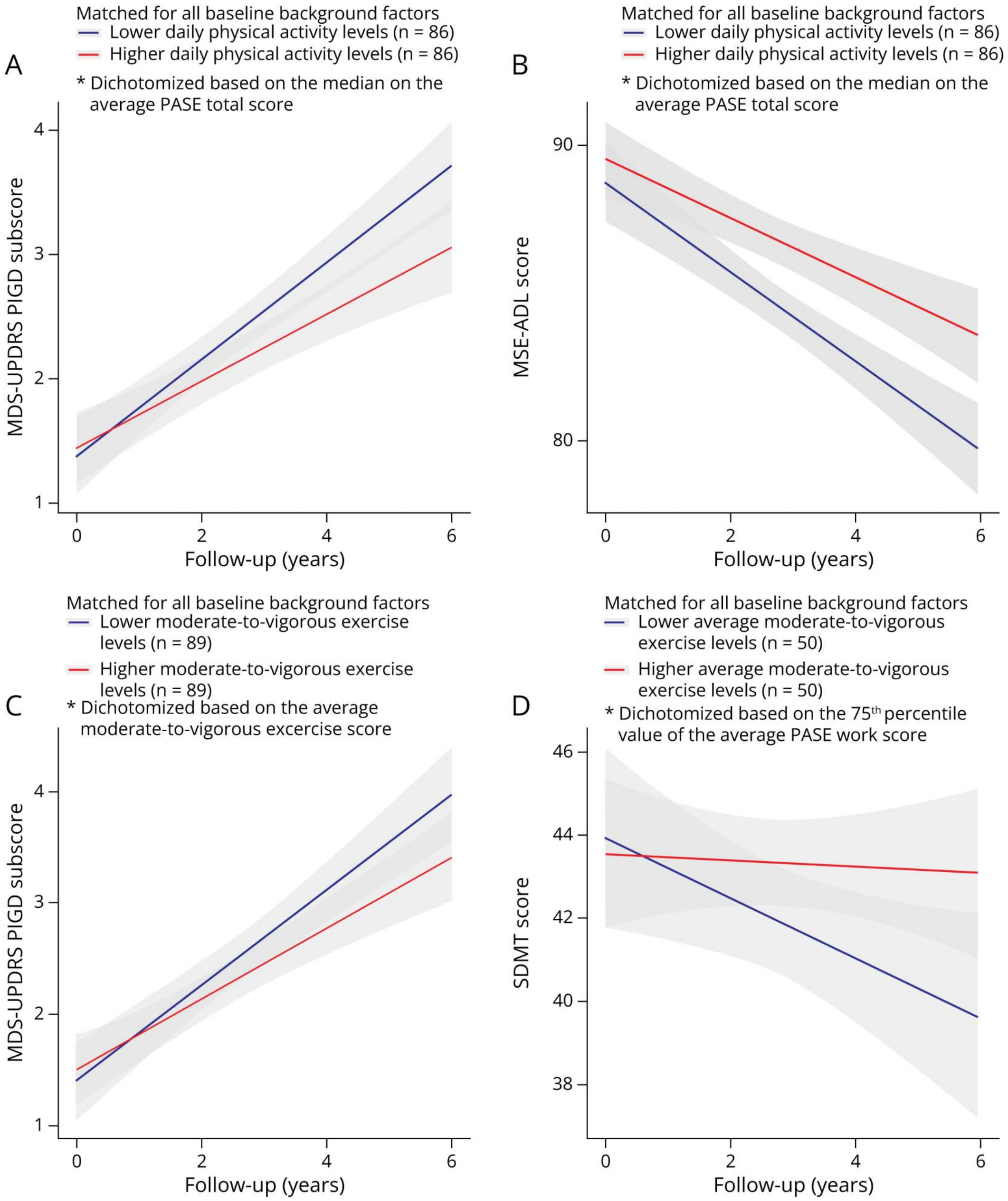
## Visualization and Confirmation of the Results Using Propensity Score Matching

Finally, to visualize and confirm the results, we conducted propensity score matching to match all background factors other than regular physical activity levels between the 2 groups. After propensity score matching based on the median of the average PASE total score over the years (175.0), both the higher and lower overall regular physical activity groups consisted of 86 patients with PD (Figure 3A) and were matched such that standardized mean differences of all background variables fell not only well within a modest cutoff of 0.25 but also within strict cutoff of 0.1 (Figure 3B).[42] Baseline clinical characteristics of these 2 groups are summarized in Table 3.

We then applied a multivariate linear mixed-effects model with an interaction term to these 2 groups and visually confirmed that the average levels of overall regular physical activity were associated with slower progression of the PIGD subscore and MSE-ADL score (PIGD subscore: $\beta_{\text{interaction}} = -0.10$ [bootstrap 95% CI −0.20 to −0.02], $t = -2.2$, Bonferroni-corrected $p = 0.03$; MSE-ADL score: $\beta_{\text{interaction}} = 0.15$ [bootstrap 95% CI 0.06–0.24], $t$ value = 3.5, Bonferroni-corrected $p < 0.01$) (Figure 4, A and B), although the interaction effect did not reach statistical significance in SDMT score ($\beta_{\text{interaction}} = 0.05$ [bootstrap 95% CI −0.01 to 0.11], $t = 1.4$, Bonferroni-corrected $p = 0.46$).

We also conducted propensity score matching based on the median of the average PASE moderate to vigorous exercise score over the years (0.33; eFigure 2, links.lww.com/WNL/B703), which roughly corresponds to a level of moderate to vigorous exercise of 1 to 2 hours on 1 to 2 d/wk. We were then able to visually confirm that higher moderate to vigorous exercise levels were significantly associated with slower progression of the PIGD subscore ($\beta_{\text{interaction}} = -0.10$ [bootstrap 95% CI −0.18 to −0.02], $t = -2.5$, $p = 0.01$) (Figure 4C). Furthermore, additional propensity score matching based on the median of the average PASE household score over the years (3.88) also confirmed that higher household activity was significantly associated with slower decline of the MSE-ADL

**Figure 4** Interaction Effects of Different Type of Regular Physical Activity Levels on Declines in Postural and Gait Function, ADL, and Processing Speed After Propensity Score Matching



In propensity score–matched groups with higher and lower overall levels of regular physical activity, we plotted temporal changes in Movement Disorders Society–sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Postural Instability/Gait Disturbance (PIGD) subscore (A) and Modified Schwab & England Activities of Daily Living (MSE-ADL) score (B). We also plotted temporal changes in the MDS-UPDRS PIGD subscore in propensity score–matched groups with higher and lower moderate to vigorous exercise levels (C) and in the Symbol Digit Modalities Test (SDMT) score in propensity score–matched groups with higher and lower work-related activity levels (D). Note that the temporal changes in these scores were visually and statistically different between 2 groups. Solid lines represent regression lines, and shaded areas represent 95% confidence intervals of regression lines.

subscore ($\beta_{\text{interaction}}$ = 0.12 [bootstrap 95% CI 0.03–0.20], $t$ = 2.8, $p$ < 0.01). For work-related activity, if we conducted propensity score matching based on the 75th percentile value of the average PASE work score over the years (32.5; eFigure 3), which roughly corresponds to a level of 15.5 hours of work (i.e., paid work or volunteer activities that require at least some physical activity such as walking) per week, it was confirmed that higher work-related activity was significantly associated with slower decline of the SDMT subscore ($\beta_{\text{interaction}}$ = 0.10 [bootstrap 95% CI 0.01–0.19], $t$ = 2.2, $p$ = 0.03) (Figure 4D).

## Discussion

This longitudinal observational study revealed that higher regular physical activity levels, only when maintained, were robustly associated with slower deterioration of several clinical parameters in patients with PD. Furthermore, it was also revealed that different types of activities may have different effects on the disease course of PD. Specifically, habits of moderate to vigorous exercise were preferentially associated with slower decline in postural and gait function, work-related activities were associated mainly with slower decline in processing speed, and household activities were associated particularly with slower decline in ADL. The strengths of our study are as follows: (1) our study had the longest follow-up period compared to previous observational studies that included objective evaluations of motor and cognitive function; (2) our study evaluated the different effects of different types of physical activity; (3) the robustness of our results was confirmed by computing bootstrap 95% CIs and conducting sensitivity analyses; and (4) the validity of our results even after comprehensive adjustment for all other baseline clinical parameters using propensity score matching reduced the likelihood that the observed interaction effects merely reflect differences in inherent disease traits.

Previous observational studies have preferentially focused on the effect of baseline physical activity levels and have shown that high baseline exercise habits and regular overall physical activity levels are associated with better clinical course of PD over a few years.[13-17] Therefore, we were initially surprised by our observation that not their baseline level but the maintenance of their level is the key factor associated with better clinical course of PD over a longer period of time. However, given the gradual decline in physical activity levels in patients with PD (Figure 1A) and the reported gradual decline in the effectiveness of interventional exercise,[43,44] it seems quite plausible that the focus should be on a sustained increase in exercise and regular physical activity levels to improve long-term clinical outcomes.

Another finding of our study is that different types of regular physical activity might have different effects on the course of PD, which is consistent with a recent meta-analysis of interventional physiotherapy studies that have shown different effects of different types of physiotherapy.[12,45] Regarding the mechanism underlying this result, previous studies have provided important clues. First, in the PASE questionnaire, several activities that require balance such as dancing, fencing, and aerobics were cited as examples of moderate to severe exercise. Thus, the observed association between habits of moderate to vigorous exercise and slower decline in posture and gait functions should be consistent with previous studies showing that balance training preferentially improves these functions.[12] Considering that very high-intensity aerobic training seems to be crucial to improve the global motor function,[10] it can also be considered that the intensity of exercise was insufficient to show any benefits in the progression of global motor function in this study. Second, previous studies have suggested that cognitive levels of jobs correlate with better processing speed and that processing speed is one of the most frequently improved domains by cognitive rehabilitation in PD.[46,47] Therefore, although the PASE questionnaire quantifies only the working hours per week but not the cognitive levels of each job, we speculate that work-related cognitive tasks may be behind the observed association between work-related activities and slower decline in processing speed. Finally, the observed association between household activities and slower decline in ADL might possibly suggest that becoming familiar with household chores is important for maintaining high ADL over time.

We believe that our findings have important implications for daily clinical practice and future clinical trials. First, they highlight the importance of supporting patients with PD in daily clinical practice to enable them to maintain their physical activity levels. For patients with PD to maintain high physical activity levels, it is essential that they themselves are convinced of the benefits of high physical activity levels.[48] An encouraging aspect of our study for both clinicians and patients with PD is that medication-refractory symptoms such as postural instability, gait disturbance, and the impairment of processing speed might be especially susceptible to the positive effect of high regular physical activity levels.[49] Second, our result would be useful for individualized counseling on regular physical activity. Third, this finding could guide future randomized controlled trials toward greater emphasis on continuous exercise to demonstrate the disease-modifying effect of exercise. The drawbacks in conducting such a randomized controlled trial include the challenges in the motivation and time required for long-term participation in an interventional exercise program.[9,50] In this context, recent advances in mobile applications (apps) that enable health professionals to remotely supervise and keep motivating patients show promises. One recent study has shown that mobile apps can be used in patients with PD,[51] and furthermore, a recent landmark randomized clinical trial has shown that performing aerobic exercises at home is feasible and efficacious under the aid of a motivational app and under remote supervision.[11] These results certainly represent a big step forward in proving the disease-modifying effect of long-term exercise on the course of PD.

The limitations of our study should be addressed. First, the study was observational in nature instead of interventional. Therefore, causal relationships between the variables could not be assessed; rather, only conclusions could be drawn regarding associations between the variables. Second, regular physical activity was quantified with the self-reported PASE questionnaire. Despite having been validated to correlate with objective measures of activity monitoring, the questionnaire itself is not objective in nature.[19-21] Third, although the PPMI study applies a strict protocol to ensure uniformity in data collection methods and timing, the PPMI dataset contains missing data and data that were excluded in our analyses. Most of those data were due to the absence of MDS-UPDRS part 3 "off" score (eFigure 1, links.lww.com/WNL/B703 and Table 2). It should be emphasized that the reason was simply that many patients were assessed for the MDS-UPDRS part 3 scale only in the "on" state; therefore, we believe that it is unlikely that those missing and excluded data would affect our results. The fact that our sensitivity analyses using the multiple imputation methods confirmed our results also supports our notion. Fourth, we did not adjust the genetic background. However, because genetic influences on regular physical activity levels have been suggested to be weak and different from those associated with PD progression,[52,53] we believe that it is unlikely that there are any genetic differences between propensity score–matched higher and lower regular physical activity groups that would influence the course of PD. It remains possible that we have overlooked some of effects of regular physical activity if it has different effects on different genotypes, as suggested by a recent important observational study showing the interaction effects among regular physical activity, *APOE* genotype, and global cognitive function.[17]

Our large-scale longitudinal observational study, with a long follow-up period and comprehensive longitudinal assessments of clinical parameters, suggests that the maintenance of high regular physical activity levels might have a long-term positive effect on the progression of disturbances in postural and gait function, processing speed, and ADL in patients with PD, with different types of activity having different effects. We believe that our finding has the potential of changing the attitude of physicians regarding exercise counseling in patients with PD. Furthermore, the present study could serve as a guide for future randomized controlled trials with greater emphasis on sustained exercise in patients with PD.

## Acknowledgment

This work was supported by JST [Moonshot R&D] [Grant Number JPMJMS2024]. PPMI, a public-private partnership, is funded by the Michael J. Fox Foundation for Parkinson's Research and funding partners, including Abbvie, Avid, Biogen, Bristol-Myers Squibb, Covance, GE Healthcare, Genentech, GlaxoSmithKline, Lilly, Lundbeek, Merck, Meso Scale Discovery, Pfizer, Piramal, Roche, Servier, Teva, UCB, and Golub Capital. The authors thank Dr. Takahiro Kamada for inspiring them to do this study. He died in January 2019, and they dedicate this article to his memory.

## Study Funding

This work was supported by JST [Moonshot R&D] [Grant Number JPMJMS2024].

## Disclosure

R. Takahashi reports grants and personal fees from Takeda Pharma, Boeringer Ingelheim, Dainippon Sumito Pharma, Kyowa-Kirin Pharma, Eisai Pharma, Otsuka Pharma, Novartis, Sanofi, Kan Institute, and Nihon Medi-physics; grants from Astellas Pharma; personal fees from Abbvie, Mylan, JBO, Sanwa Kagaku, FP Pharma, Tsumura, Kissei, Chugai Pharma, and Biogen, outside the submitted work. The remaining authors (K. Tsukita and H. Sakamaki-Tsukita) report no disclosures. Go to Neurology.org/N for full disclosures.

## Publication History

Received by *Neurology* July 9, 2021. Accepted in final form November 30, 2021.

## Appendix Authors

| Name | Location | Contribution |
|---|---|---|
| **Kazuto Tsukita, MD** | Kyoto University, Japan | Design and conceptualization of the study; acquisition, analysis, and interpretation of the data; statistical analysis; drafting of the manuscript |
| **Haruhi Sakamaki-Tsukita, MD** | Kyoto University, Japan | Design and conceptualization of the study; acquisition, analysis, and interpretation of the data |
| **Ryosuke Takahashi, MD, PhD** | Kyoto University, Japan | Design and conceptualization of the study; interpretation of the data; revising the manuscript for intellectual content |

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# Long-term Effect of Regular Physical Activity and Exercise Habits in Patients With Early Parkinson Disease

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*Neurology* 2022;98;e859-e871 Published Online before print January 12, 2022
DOI 10.1212/WNL.0000000000013218

**This information is current as of January 12, 2022**

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