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

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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 [$\beta_{interaction}$] = −0.10 [95% CI −0.14 to −0.06]), activities of daily living ($\beta_{interaction}$ = 0.08 [95% CI 0.04–0.12]), and processing speed ($\beta_{interaction}$ = 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 ($\beta_{interaction}$ = −0.09 [95% CI −0.13 to −0.05]), and work-related activity levels were primarily associated with slower deterioration of processing speed ($\beta_{interaction}$ = 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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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]

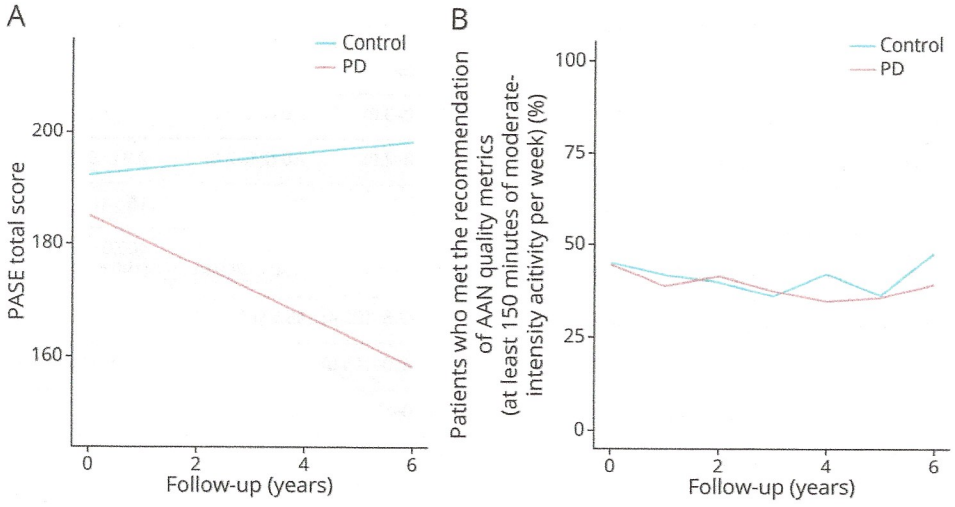
Furthermore, we used the total score of the 15-item Geriatric Depression Scale as a measure of depression,[32] total score of the Scales for Outcomes in Parkinson's Disease–Autonomic Dysfunction as a measure of autonomic symptoms,[33] total score of the Epworth Sleepiness Scale as a measure of daytime 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

**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 ($\beta$), 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 $\beta_{interaction}$ 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 *(continued)*

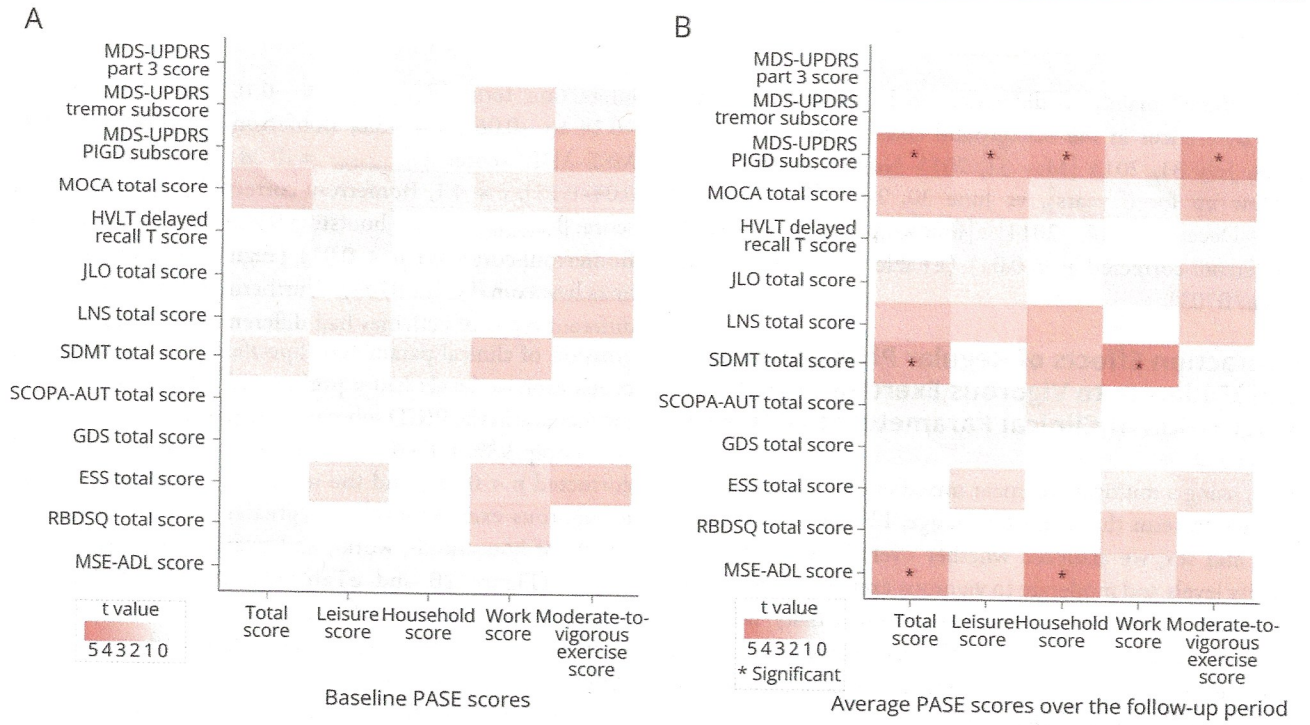
| | Follow-up year | | | | | |
|---|---|---|---|---|---|---|
| | 1 (n = 223)[a] | 2 (n = 226)[a] | 3 (n = 209)[a] | 4 (n = 191)[a] | 5 (n = 153)[a] | 6 (n = 118)[a] |
| MSE-ADL score | 90.0 (80.0–90.0) | 90.0 (80.0–90.0) | 90.0 (80.0–90.0) | 90.0 (80.0–90.0) | 80.0 (80.0–90.0) | 80.0 (80.0–90.0) |
| 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 $\rho = -0.04$ [95% CI −0.09 to 0.02], $p = 0.17$; HCs: Spearman $\rho = -0.04$ [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 $p < 0.05$).

**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: $\beta_{interaction}$ = −0.10 [bootstrap 95% CI −0.20 to −0.02], $t$ = −2.2, Bonferroni-corrected $p$ = 0.03; MSE-ADL score: $\beta_{interaction}$ = 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 ($\beta_{interaction}$ = 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 ($\beta_{interaction}$ = −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

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

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# Backward Walking in Parkinson Disease

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## Abstract

We walk backward on a daily basis, such as when backing away from the kitchen sink or stepping back from a curb as a swiftly moving bus passes. This task may be particularly difficult for individuals with PD who often fall as a result of moving or being perturbed in the backward direction (Horak et al. 2005, Bloem et al 2004). The aim of this study was to assess backward walking in individuals with PD. Both forward and backward gait were assessed in 78 people with idiopathic PD (H&Y range: 0.5–3) in the ON state, and 74 age- and sex-matched controls. In forward walking, those with PD had significantly shorter strides, lower swing percents, higher stance percents and lower functional ambulation profiles than controls. Both groups walked significantly slower and with a wider base of support during backward walking than forward walking. Additionally, in backward walking those with PD walked significantly slower with shorter strides, lower swing percents, and higher double support and stance percents, and lower functional ambulation profiles compared to controls. Those with mild to moderate PD have impaired forward and backward walking, but differences between those with and without PD are more pronounced in backward walking.

## Keywords

Gait; Backward; Parkinson Disease

## Introduction

Falls are common among individuals with Parkinson disease (PD), a progressive neurodegenerative movement disorder affecting more than 1 million people in the United States. Fall-related hip fractures in the United States cost approximately $192 million annually.[1, 2] Seventy percent of patients experienced a fall within a one year period, with 50% of fallers experiencing a recurrent fall in the subsequent year 3. A meta-analysis of fall rates revealed that in three months, half of a large cohort of those with PD experienced a fall. In fact, patients with no previous fall history had a 21% risk of falling in this same time period 4. Many falls occur from backward perturbation or while moving backward [4,5]. Those with PD have difficulty modulating gait parameters according to task, and locomotion is a complex multi-directional activity; therefore gait analysis should include functional locomotor tasks beyond straight walking [6]. No study has examined backward walking in PD.

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We walk backward daily, such as when backing away from a sink, or stepping back from a curb as a swiftly moving bus passes. Laufer et al. (2005) noted that an elderly cohort walked slower backward than a younger group. Backward gait was also characterized by lesser cadence, increased double support time, and shorter stride length and swing phase [7]. Unable to increase stride length while walking backward, the elderly increased speed only by increasing cadence. Possibly those with PD are further impaired while walking backward, since without visual cues it relies more heavily on proprioception than forward walking.8 Postural instability in PD may be related to proprioceptive disturbances attributed to abnormal processing of proprioceptive signals in the basal ganglia 9· 10. Those with PD excessively activate antagonist muscles when posturally perturbed, particularly in the lateral and backward directions [11]. Postural abnormalities are most noted in response to backward perturbations because counteracting muscle torques generate stiffening in the ankle and trunk. PD medication does little to improve pitch plane abnormalities [12], and pronounced backward instability in PD is levodopa-resistant and not helped by subthalamic nucleus stimulation [13]. This study aimed to quantify backward walking in those with mild to moderate PD in comparison to a matched control group.

## Methods

This work was approved by the Human Research Protection Office at Washington University in St. Louis. All participants provided written informed consent before participation.

### Participants

Participants were recruited from the St. Louis community through advertisement at support groups and community events and from a database that follows some 2000 people with PD. While some participants self-identified, most were directly recruited via telephone, and some were randomly asked to participate at a public site distant to the laboratory. Data files were coded for participant confidentiality.

Seventy-eight people with PD (mean age = 65.1±9.5 years, Female: 28%) and 74 age- and sex-matched controls (mean age = 65.0±10.0 years, Female: 23%) participated. Participants were excluded if they had history or evidence of neurological deficit other than PD. All participants with PD had a diagnosis of idiopathic PD using criteria for clinically defined "definite PD" 14·15·16, demonstrated clear benefit from levodopa, were tested ON medications at a time of self-determined optimal performance, and could walk at least 3 meters with or without an assistive device. Participants were evaluated using the Unified Parkinson's Disease Rating Scale Motor Subscale 3 (UPDRS) 17· 18 and the Berg Balance Scale (BBS) 19. Fallers were those who reported one or more falls in the preceding six months. Freezing status was determined by the Freezing of Gait questionnaire (FOG) 20. Participants were considered freezers if they had a score >1 on Item 3 on the FOG, indicating freezing frequency of more than once per week 21.

### Kinematics

Forward and backward gait were measured using a 5m instrumented, computerized GAITRite walkway (CIR Systems, Inc., Havertown, PA). Participants were requested to walk at their normal pace forward (FW) to accustom themselves to the mat, and then backward (BW), performing three trials of each direction. Participants were given adequate rest time and allowed to sit between trials. No participants reported fatigue, likely because of the short walking distance and limited number of trials. Results from trials of each direction were averaged. Primary variables of interest were gait velocity, stride length, cadence, heel to heel base of support (BOS), double support percent, swing and stance percent, and functional ambulation profile (FAP, a.k.a. Functional Ambulation Performance). The FAP is a valid and reliable

numerical representation of gait performance[22] that distinguishes between people with and without PD 23. FAP values quantify gait variability and comprise the linear relationship of step length/leg length ratio to step time when the velocity is normalized to leg length (see Appendix for more detail).

### Statistical Analyses

Two way repeated measures ANOVAs (two subject groups X two conditions) with Holms-Sidak post-hoc tests determined statistical significance when comparing those with PD to controls. Pearson's Product Moment Correlations determined relationships between disease severity or balance and FW or BW velocity. Independent t-tests determined significant differences between freezers and non-freezers. Mann Whitney Rank Sum tests were used for non-parametric data. The level of significance was set at p=0.05.

## Results

The PD group's Hoehn & Yahr scores ranged from 0.5–3, (1 each at stages 0.5 and 1, 11 at stage 1.5, 49 at stage 2, 8 at stage 2.5 and 8 at stage 3). They had an average UPDRS motor subscale 3 score of 27.5 ± 9.2 and disease duration of 8.2 ± 5.0 years. Fifty percent of those with PD had a history of falls, and 45% were freezers.

### Gait Parameters of Forward and Backward Walking: Individuals with PD versus Age- and Sex-Matched Controls

Table 1 summarizes results. If significant interactions are presented, there are also significant main effects of condition and group.

**Velocity**—There were significant two way interactions among group and condition for velocity (interaction: $F(1,150)=22.352$, $p<0.001$). In FW, the groups walked at similar velocities. In BW, those with PD walked slower than controls ($p<0.001$). Both groups walked significantly slower during BW than FW ($p<0.001$).

**Stride Length**—There were significant two way interactions among group and condition for stride length (interaction: $F(1,150)=28.232$, $p<0.001$). Those with PD walked with a significantly shorter stride length than controls in FW ($p=0.023$) and BW ($p<0.001$). Both groups walked with significantly shorter strides during BW than FW ($p<0.001$).

**Swing Percent**—There were significant two way interactions among group and condition for swing percent (interaction: $F(1,150)=18.818$, $p<0.001$). Those with PD walked with lesser swing percent than controls in both FW ($p=0.019$) and BW ($p<0.001$). Lesser swing percent was noted in BW when compared to FW in both those with PD ($p<0.001$) and controls ($p=0.024$).

**Stance Percent**—There were significant two way interactions among group and condition for stance percent (interaction: $F(1,150)=20.223$, $p<0.001$). Those with PD walked with greater stance percent than controls in FW ($p=0.023$) and BW ($p<0.001$). Greater stance percent was noted in BW when compared to FW in both those with PD ($p<0.001$) and controls ($p=0.014$).

**Double Support Percent**—There were significant two way interactions between group and condition for double support percent (interaction: $F(1,150)=8.847$, $p=.003$). In FW, the groups walked with a similar double support percentage ($p=0.065$). In BW, those with PD walked with greater double support percentage than Controls ($p<0.001$). More double support percent during BW than FW was noted in both those with PD ($p<0.001$) and controls ($p<0.005$).

**BOS**—There were no significant two way interactions between group and condition for BOS ($F(1,150)=2.005$, $p=0.159$) but there was a significant main effect of condition ($F(1, 150) =556.438$). Both groups walked with a significantly wider BOS during BW than FW ($p<0.001$).

**Cadence**—There were no significant two way interactions between group and condition for cadence ($F(1,150)=0.942$, $p=0.333$) but there was a significant main effect of group ($F(1, 150) =4.838$). Those with PD walked with a greater cadence than Controls overall($p=0.029$), but were not different form Controls within FW or BW alone.

**FAP**—There were significant two way interactions among group and condition for FAP. (interaction: $F(1,150)=18.433$, $p<0.001$). Those with PD had significantly lower FAP values than controls in both FW ($p=0.022$) and BW ($p<0.001$). Both groups had significantly lower FAP values during BW than FW ($p<0.001$).

**Variability of Gait Measures**—There were significant two way interactions among group and condition for stance percent variability ($F(1,150)= .554$ , $p=0.034$). Controls and those with PD had similar amounts of stance percent variability in FW ($p=0.849$). Controls had similar amounts of stance percent variability in BW and FW ($p=0.089$). Those with PD had more stance percent variability in BW than Controls ($p=0.006$). In those with PD stance percent variability was greater in BW than in FW ($p<0.001$).

There was a significant main effect of condition for other measures of variability but no significant interactions. BW was more variable than FW in stance percent ($F(1, 150)=21.071$), stride length ($F(1,150)=45.135$), , and swing percent ($F(1,150)= .686$, $p=0.002$).

**Correlations of UPDRS or BBS and Forward or Backward Velocity**—As UPDRS scores increased, BW velocity decreased ($r=-0.290$, $p=0.010$) but UPDRS was uncorrelated with FW velocity ($r=-0.126$, $p=0.272$). As FW velocity increased, BW velocity increased ($r=0.766$, $p<0.001$). As BBS scores increased, both BW ($r=0.538$) and FW ($r=0.486$) velocity increased ($p<0.001$). No significant relationships were found between duration of PD and FW or BW ($r=0.012$, $p=0.917$; $r=-0.200$, $p=0.079$)

## Comparison of Freezers and Non-Freezers

On the BBS, freezers (mean: $46.8 \pm 0.85$) scored significantly lower ($p=0.003$), than non-freezers (mean: $50.0 \pm 0.61$), and had PD for longer (Freezers: $10.5 \pm 1.00$, Non-freezers: $6.4 \pm 0.57$, $p=0.002$), but did not differ from non-freezers in disease severity (UPDRS Freezers: $29.2 \pm 1.63$, Non-freezers: $26.2 \pm 1.33$, $p=0.150$). No one exhibited freezing during testing. Table 2 summarizes results for freezers vs. non-freezers.

**Forward Walking**—Freezers and non-freezers were similar in FW FAP ($p=0.097$), velocity ($p=0.106$), cadence ($p=0.768$), stride length ($p=0.075$), and BOS ($p=0.195$). Freezers had significantly lower swing percent ($p=0.007$) and significantly greater double support ($p=0.012$) and stance percent ($p=0.007$) than non-freezers. Freezers and non-freezers were similar in FW variability for stride length ($p=0.053$). Freezers were more variable in stance ($p=0.008$) and swing percent ($p<0.001$).

**Backward Walking**—Freezers and non-freezers were similar in BW velocity ($p=0.091$), cadence ($p=0.422$), double support percent ($p=0.065$), and BOS ($p=0.321$). In BW, freezers had significantly lower FAP scores ($p=0.027$), stride length ($p=0.032$), swing percent ($p=0.040$), and significantly greater stance percent ($p=0.031$) than non-freezers. Freezers and non-freezers were similar in BW variability of stride length ($p=0.325$). Freezers were more variable in stance percent ($p=0.010$) and swing percent ($p=0.013$).

## Discussion

This is the first study to examine BW in people with PD. Previous work showed that healthy younger and older adults walk slower backward than forward but alter their cadence little for different walking directions [24, 7]. The elderly show diminished stride length when walking backward [7]. Our PD group exhibited similar but more pronounced changes during backward walking compared to older controls. Prior work has also shown that BW is more variable than FW [25]. On the FAP measure lower values indicate more variable stride to stride performance. Our results are thus in keeping with those of Winter et al. (1989), suggesting that all participants were more variable walking backward than forward. Variability was most evident in stance percentages of the PD group compared to Controls. Freezers had longer disease duration and were more balance impaired, which may explain their slightly poorer performance and greater variability than non-freezers.

Curiously, our PD participants did not walk slower than controls in FW. Possibly our participants with PD experienced a testing effect, and could achieve nearly normal magnitudes of speed through focused attention on gait as our participants knew their performance was being monitored [26, 6]. Although our PD group walked at a similar velocity to controls, their stride length, swing and stance percents and FAP values were impaired in FW compared to controls. This agrees with current research demonstrating that gait speed may be virtually intact, while other spatiotemporal features of FW are affected in even de novo PD [28].

The present study demonstrates that individuals with PD have BW deficits that surpass FW deficits. Similarly, individuals with PD with normal or mildly impaired FW demonstrate greater impairments when turning [29,30]. Crenna et al. (2007) propose that neural systems that are separate from FW mechanisms, and more vulnerable to the effects of PD, likely mediate turning. This may parallel BW, as recent work suggests the presence of separate control systems for FW and BW [31, 32]. If FW and BW are controlled by separate neural systems, these systems could be differentially affected by PD. The present study suggests the backward system could be impacted earlier in the disease process.

Increased UPDRS values correlated with a decrease in BW velocity. Fall rates also increased with UPDRS values [4]. BW performance is predictive of walking difficulty in high-functioning older adults and might prove useful for those with PD [33]. Assessment of BW may be an important clinical tool, as BW impairments might be related to the propensity for backward falls. BW observation may be more illustrative of the degree to which the basal ganglia are impaired than is FW. In fact, the basal ganglia appear important for optimizing patterns of postural muscle activation for the proper motor pattern in task or environmental changes [11]. Finally, subthalamic nucleus stimulation does not improve levodopa-resistant postural instability [13]. While deep brain implants have been effective on multiple parkinson-related impairments, BW could be especially useful as a test for further improvements or declines in those with STN stimulation and postural instability.

BW could be a rehabilitative component. In fact, multidirectional gait and step training reduced fall incidence and improved gait in people with PD [34]. Training BW could provide more cardiovascular benefit than forward walking, as energy expenditure is higher during BW than during FW at matched speed [35, 36]. Training BW improves cardiovascular fitness and BW efficiency in controls [37,38]. Future studies should examine relationships between BW performance, postural instability, and the effects of increasing task complexity, such as dual tasking, on BW versus FW. Research that explores rehabilitative possibilities, such as employing BW in gait and step training, is needed.