Research article

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

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ABSTRACT

Objective: Owing to the lack of long-term observations and/or comprehensive adjustment for confounding factors, reliable conclusions regarding long-term effects of exercise and regular physical activity in Parkinson's 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 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 through 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 the propensity score matching to match for all baseline background factors.

Results: 237 early PD patients [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 the 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 to 0.12)], and processing speed [$\beta_{interaction}$ = 0.05 (95% CI, 0.03 to 0.08)] in PD patients. 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 to 0.09)]. Multiple imputation and propensity score matching confirmed the robustness of our results.

Conclusions: 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 (NCT01176565). A link to trial registry page is https://clinicaltrials.gov/ct2/show/NCT01141023.

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

INTRODUCTION

Parkinson's disease (PD), in which abnormal α-synuclein aggregates play a key pathological role, is the second most common neurodegenerative disease after Alzheimer's disease.[1,2] Furthermore, PD is the fastest increasing neurological 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 non-motor 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 PD patients and clinicians is that there is still no disease-modifying treatment to slow the disease's progression.[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, two rigorously designed randomized clinical trials have confirmed that aerobic exercise can improve the 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 (less than 6 months).[12] Recent observational studies have suggested that exercise habits at the 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 also 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 the baseline are associated with slower motor and cognitive decline over a few years.[14–17] However, again, the short follow-up period and/or 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 PD patients.

The Parkinson's Progression Markers Initiative (PPMI) is a large international multicenter study [clincaltrials.gov (NCT01141023)] that has been under way since 2012; it aims to gain greater understanding of the disease course of PD and identify the disease's 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 aged over 65 years.[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 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 an observational cohort study using data from PPMI study, which were obtained from the PPMI database (http://www.ppmi-info.org/data) 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), de novo patients with PD who were not on dopaminergic medication and exhibited presynaptic dopaminergic terminal loss as confirmed by dopamine transporter (DAT) 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 DAT imaging. Further details of the study protocol are available on the PPMI website (http://www.ppmi-info.org/study-design).

Among PD patients registered in the PPMI database, the participants in this longitudinal study were selected based on the following criteria. First, at least three sets of PASE questionnaire data should be available because the effect of regular physical activity over subsequent two years were 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 III 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 PD patients 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 de novo PD patients, and annually afterward.[16] The 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 were 5 years [interquartile range (IQR): 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 their local ethic committee prior to study initiation, and written informed consent was obtained from all subjects prior to participation. Our study strictly adheres to the publication policy in the PPMI study (https://www.ppmi-info.org/documents/ppmi-publication-policy.pdf) 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 using 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 that 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 PD patients should consist of at least 150 minutes of moderate-intensity activity per week.[22] 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 Hoen-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 III score.[23] 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/Gait Disturbance (PIGD) and tremor subscores.[24]

We assessed global cognitive function using the Montreal Cognitive Assessment (MOCA).[25] To assess the sub-domains of cognitive function, we employed the delayed recall T score of the Hopkins Verbal Learning Test-Revised (HLVT-R) as a measure of verbal recent memory,[26] total score of the Letter-Number Sequencing test (LNS) as a measure of working memory,[27] and total score of the Symbol Digit Modalities Test (SDMT) as a measure of processing speed.[28]

Furthermore, we used the total score of the 15-item Geriatric Depression Scale (GRS) as a measure of depression,[29] total score of the Scales for Outcomes in Parkinson's Disease-Autonomic Dysfunction (SCOPA-AUT) as a measure of autonomic symptoms,[30] total score of the Epworth Sleepiness Scale (ESS) as a measure of daytime sleepiness,[31] total score of the REM sleep Behavior Disorder Screening Questionnaire (RBDSQ) as a measure of dream-enacting behavior,[32] and Modified Schwab & England Activity of Daily Living scale (MSE-ADL) as a measure for ADL.[33] For LEDD calculation, the LEDD of each drug was calculated by multiplying its daily dose by its conversion factor,[34] 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 (http://www.ppmi-info.org).

Statistical analyses

K.T., who is certified by the Japan Statistical Society, primarily conducted statistical analyses using self-made R scripts for the statistical software R (version 4.0.5, available from https://www.R-project.org). We performed the Wilcoxon rank sum test, Pearson's chi-square test, and Spearman's rank correlation, as appropriate.

To adjust for covariates and examine the interaction effect, we used the multivariate linear mixed-effects model with an interaction term since each participant provides several data points.[35] In our model, each clinical parameter represented a response 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, and an interaction effect term between the first two predictor variables, and a predictor variable with random effects was each subject identification number. To make the result more interpretable by putting different variables on the same scale and obtain standardized fix-effects coefficients (β), all continuous variables were Z-transformed in advance by subtracting the mean and dividing by the standard deviation. We primarily used the likelihood ratio test as a means to obtain *P* value in a multivariate linear mixed-effects model.[35] 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,[36] we confirmed the robustness of our result by computing 95% confidence intervals (CIs) for each $\beta_{interaction}$ estimate using the bootstrapping method (1000 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 result. For this purpose, after we dichotomized PD patients into lower and higher regular physical activity group using the median or 75th percentile level of regular physical activity, propensity score matching was performed to obtain two 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 standard deviation of the logit of the propensity score, one-to-one matching using the nearest neighbor method without replacement was performed.[37,38] The balance of covariates between two propensity score-matched groups was evaluated by standardized mean differences.[39]

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

Data availability

All data used in this study are available in the PPMI database (http://www.ppmi-info.org/data). The R scripts used in this study is deposited in Dryad and will be freely available upon publication (https://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 Parkinson disease was associated with slower decline of several clinical parameters.

RESULTS

Clinical characteristics of PD patients

At the baseline, we finally included 237 PD patients [age, 63.0 (56.0–70.0) years; the proportion of males, 69.2 %; disease duration, 3.0 (3.0–5.0) years; LEDD, 100.0 (0.0–300.0) mg; MDS-UPDRS part 3 score, 25.0 (18.0–34.0); MOCA total score, 27.0 (25.0–29.0)]. The flowchart in eFigure 1 shows the number of PD patients at each stage of the patient inclusion process in our study.

At the baseline, compared to 158 HCs with the same inclusion criteria [age, 64.0 (58.0–71.0) years; the proportion of males, 62.0 %], PD patients showed significantly greater impairment in motor, cognitive, and autonomic functions (table 1). However, regular physical activity levels and moderate-to-vigorous exercise levels were not significantly different between the two groups [Total PASE score: 175.0 (110.5–250.5) (PD) vs. 182.2 (131.4–242.5) (HCs), P = 0.28; moderate-to-vigorous exercise levels: 0.11 (0.00–0.75) (PD) vs. 0.25 (0.00–0.93) (HCs), P = 0.38; participants who met AAN quality metrics, 44.3 % (PD) vs. 44.9 % (HCs), P = 0.90].

During the follow-up period, overall regular physical activity level of PD patients gradually decreased with the PASE total score decreasing by 4.5 points per year [95% CI, -7.3 to -1.7; Spearman's rho = -0.08 (95% CI, -0.14 to -0.03), P < 0.01)], while no significant change was observed longitudinally in HCs [Spearman's 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 PD patients and HCs, but this trend did not reach statistical significance [PD, Spearman's rho = -0.04 (95% CI, -0.09 to 0.02), P = 0.17; HCs, Spearman's 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; HCs, 44.9 % (baseline) vs. 47.8 % (after 6 years), P = 0.73] (figure 1B).

The temporal change in all clinical variables of PD patients are summarized in table 2. The number of PD patients 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. Since the original PPMI study is still ongoing and the current data is downloaded on April 2021, the decline in the number of PD patients over time in this study should be attributed mainly to differences in baseline dates, rather than differences in the background characteristics [Baseline

dates, 2013/07/31 (2013/05/31–2013/11/30) (follow up for 6 years) vs. 2014/06/30 (2014/02/28–2014/12/16) (follow up for 5 years or less), Bonferroni-corrected $P < 0.01$]. (eTable 1)

Interaction effects of regular physical activity and moderate-to-vigorous exercise levels on progression of clinical parameters in PD patients

Next, using a multivariate linear mixed-effects model with an interaction term that adjusted for age, LEDD, disease duration, and sex, we first analyzed whether overall regular physical activity levels and moderate-to-vigorous exercise levels as well as leisure-, household-, and work-related activity levels at the 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 ($\beta_{interaction}$) = -0.10 (bootstrap 95% CI, -0.14 to -0.06), t value = -5.0, Bonferroni-corrected $P < 0.01$; MSE-ADL score, $\beta_{interaction} = 0.08$ (bootstrap 95% CI, 0.04 to 0.12), t value = 4.1, Bonferroni-corrected $P < 0.01$; SDMT score, $\beta_{interaction} = 0.05$ (bootstrap 95% CI, 0.03 to 0.08), t value = 3.7, Bonferroni-corrected $P < 0.01$] (figure 2B, eTable 2). 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 [$\beta_{interaction}$ = -0.09 (bootstrap 95% CI, -0.13 to -0.05), t value = -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, eTable 2). Work-related activity levels, on the other hand, had an interaction effect primarily on the progression of processing speed decline [$\beta_{interaction} = 0.07$ (bootstrap 95% CI, 0.04 to 0.09), t value = 4.7, Bonferroni-corrected $P < 0.01$], and the largest interaction effect of housework-related activities was seen on the deterioration of ADL [$\beta_{interaction} = 0.09$ (bootstrap 95% CI, 0.05 to 0.12), t value = 4.7, Bonferroni-corrected $P < 0.01$] (figure 2B, eTable 2). Furthermore, in addition to the bootstrap 95% CIs as described above, sensitivity analyses using the multiple imputation method for missing data also confirmed the robustness of our model (eTable 2).

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 two groups. After propensity score matching based on the median of the average PASE total score over the years (= 175.0), higher and lower overall regular physical activity groups both consisted of 86 PD patients (figure 3A) and were matched such that standardized mean differences of all background variables not only fell well within a modest cutoff of 0.25, but also within strict cutoff of 0.1 (figure 3B).[39] Baseline clinical characteristics of these two groups are summarized in table 3.

We then applied a multivariate linear mixed-effects model with an interaction term to these two 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 value = -2.2, Bonferroni-corrected P = 0.03; MSE-ADL score, $\beta_{interaction}$ = 0.15 (bootstrap 95% CI, 0.06 to 0.24), t value = 3.5, Bonferroni-corrected P < 0.01] (figure 4A and 4B), 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 value = 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), which roughly corresponds to a level of moderate-to-vigorous exercise of 1-2 hours, 1-2 days per week. 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 value = -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 subscore [$\beta_{interaction}$ = 0.12 (bootstrap 95% CI, 0.03 to 0.20), t value = 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 [$\beta_{interaction}$ = 0.10 (bootstrap 95% CI, 0.01 to 0.19), t value = 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 PD patients. 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 mainly associated with slower decline in processing speed, and household activities were particularly associated 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,[40,41] 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 novel 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.[12,42] 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.[43,44] Therefore, although PASE questionnaire only quantifies 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. To maintain high physical activity levels for PD patients, it is essential that that they themselves are convinced of the benefits of high physical activity levels.[45] An encouraging aspect of our study for both clinicians and PD patients 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.[46] 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.[9,47] In this context, recent advances in mobile 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,[48] 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, conclusions could only be drawn regarding associations between the variables. Second, regular physical activity was quantified using 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. The most of those data were due to the absence of MDS-UPDRS part 3 "off" score (eFigure 1 and table 2). It should be emphasized that this was simply because many patients were assessed for the MDS-UPDRS part 3 scale only in the "on" state and, therefore, we believe that it is unlikely that those missing and excluded data would affect our result. 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, as genetic influences on regular physical activity levels have been suggested to be weak and different from those associated with PD progression,[49,50] 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 overlook 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]

In conclusion, 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 PD patients 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.

Appendix 1: Authors

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

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FIGURE TITLES AND LEGENDS

Figure 1. Temporal changes in overall regular physical activity levels and the 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. The gray areas represent the standard error of the regression lines.

Abbreviations: PD, Parkinson's disease.

Figure 2. Summary of the interaction effect of each regular physical activity level on the decline of each function in Parkinson's disease (PD) patients

Matrices showing the degree of interaction effect of the overall level of regular physical activity and the level of different types of physical activity on the progression of each clinical parameter, as determined using the t-value calculated by 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). * indicates significant association after the Bonferroni correction (Bonferroni-corrected $P < 0.05$).

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

Figure 3. Distribution of propensity scores and balance measures after propensity score matching

At first, Parkinson's disease (PD) patients were dichotomized using the median of the average Physical Activity Scale for the Elderly (PASE) total score. After propensity score matching, higher and lower regular physical activity groups both consisted of 86 PD patients (A) and were matched such that standardized mean differences between all background factors fell within a strict cut-off of 0.1 (B).

Abbreviations: MDS-UPDRS, Movement Disorders Society-sponsored revision of the Unified Parkinson's disease rating scale; PIGD, Postural Instability and Gait Disturbance; MOCA, Montreal Cognitive Assessment; HVLT-R, Hopkins Verbal Learning Test-Revised; JLO, Judgment of Line Orientation; LNS, Letter-Number Sequencing; SDMT, Symbol Digit Modalities Test; SCOPA-AUT, Scales for Outcomes in Parkinson's Disease-Autonomic; GDS, Geriatric Depression Scale; ESS, Epworth Sleepiness Scale; RBDSQ, REM sleep Behavior Disorder Screening Questionnaire; MSE-ADL, Modified Schwab & England Activities of Daily Living scale.

Figure 4. Interaction effects of different type of regular physical activity levels on declines in postural and gait function, activity of daily living (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 ADL (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 those 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 two groups.

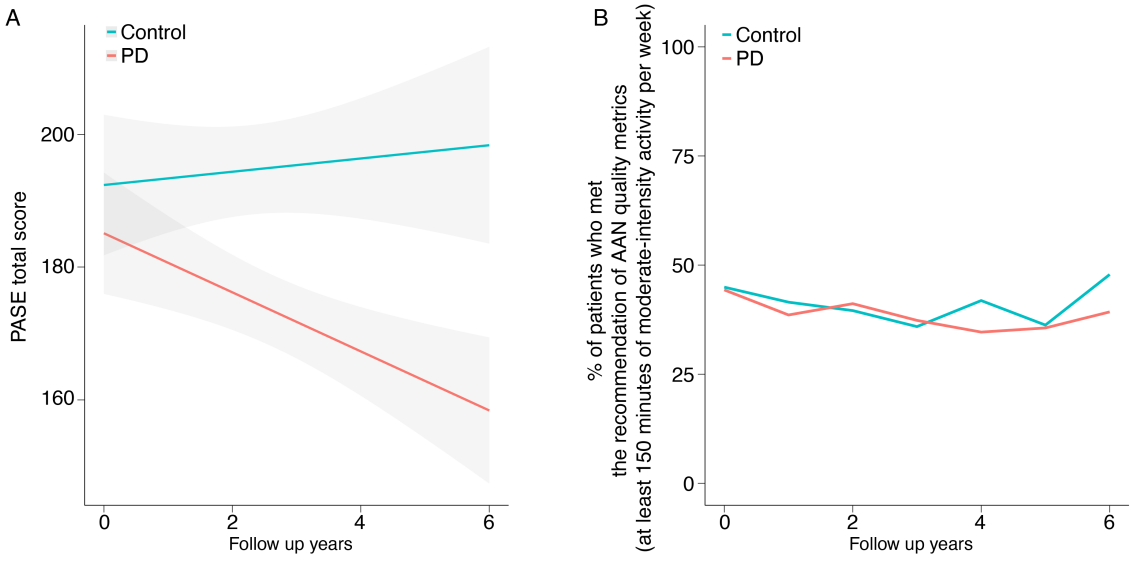

A
Control
PD
PASE total score
200
180
160
0
2
4
6
Follow up years
B
Control
PD
% of patients who met
the recommendation of AAN quality metrics
(at least 150 minutes of moderate-intensity activity per week)
100
75
50
25
0
0
2
4
6
Follow up years

Figure 1

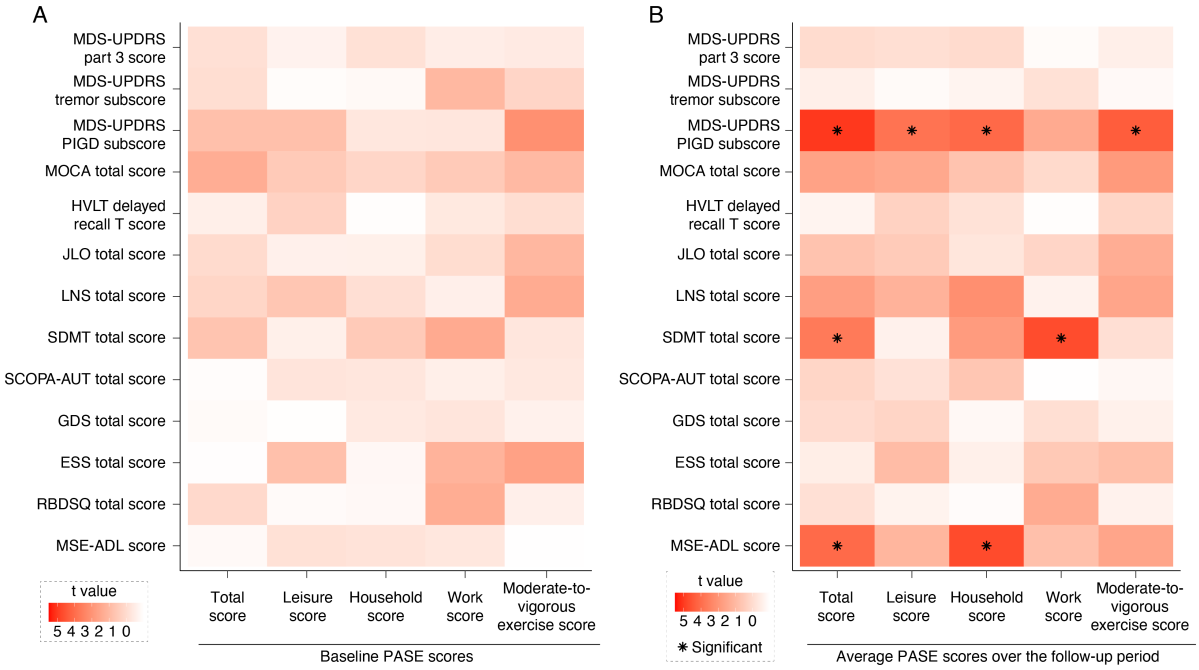

A
MDS-UPDRS part 3 score
MDS-UPDRS tremor subscore
MDS-UPDRS PIGD subscore
MOCA total score
HVLT delayed recall T score
JLO total score
LNS total score
SDMT total score
SCOPA-AUT total score
GDS total score
ESS total score
RBDSQ total score
MSE-ADL score
t value
5 4 3 2 1 0
Total score
Leisure score
Household score
Work score
Moderate-to-vigorous exercise score
Baseline PASE scores
B
MDS-UPDRS part 3 score
MDS-UPDRS tremor subscore
MDS-UPDRS PIGD subscore
MOCA total score
HVLT delayed recall T score
JLO total score
LNS total score
SDMT total score
SCOPA-AUT total score
GDS total score
ESS total score
RBDSQ total score
MSE-ADL score
t value
5 4 3 2 1 0
* Significant
Total score
Leisure score
Household score
Work score
Moderate-to-vigorous exercise score
Average PASE scores over the follow-up period

Figure 2

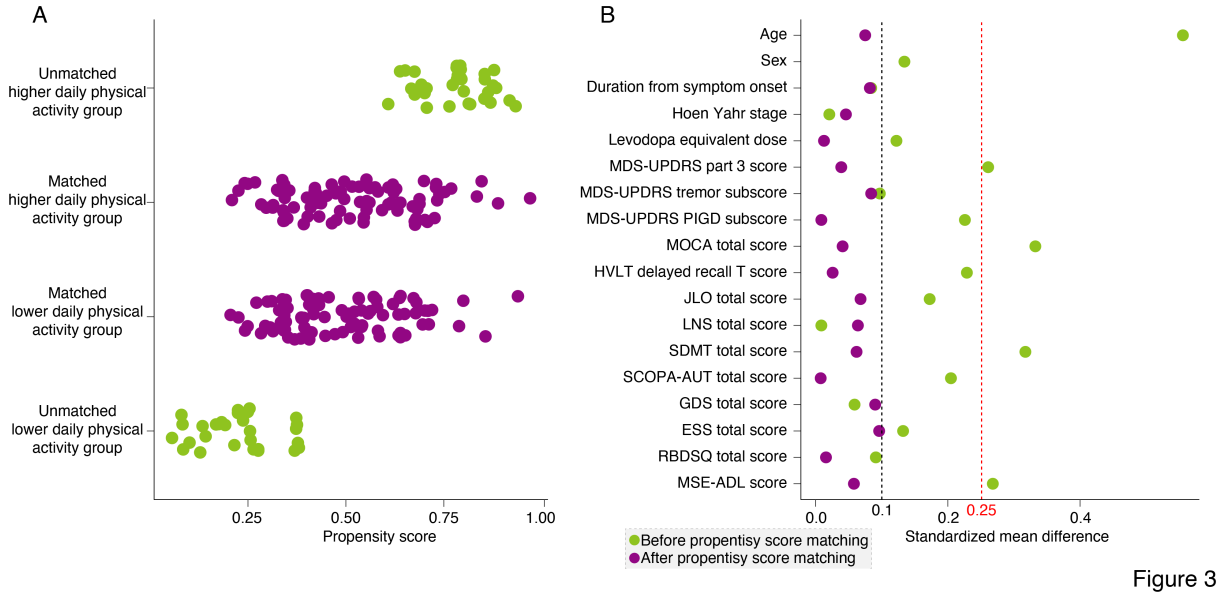

A
Unmatched higher daily physical activity group
Matched higher daily physical activity group
Matched lower daily physical activity group
Unmatched lower daily physical activity group
0.25
0.50
0.75
1.00
Propensity score
B
Age
Sex
Duration from symptom onset
Hoen Yahr stage
Levodopa equivalent dose
MDS-UPDRS part 3 score
MDS-UPDRS tremor subscore
MDS-UPDRS PIGD subscore
MOCA total score
HVLT delayed recall T score
JLO total score
LNS total score
SDMT total score
SCOPA-AUT total score
GDS total score
ESS total score
RBDSQ total score
MSE-ADL score
0.0
0.1
0.2
0.25
0.4
Standardized mean difference
Before propentisy score matching
After propentisy score matching

Figure 3

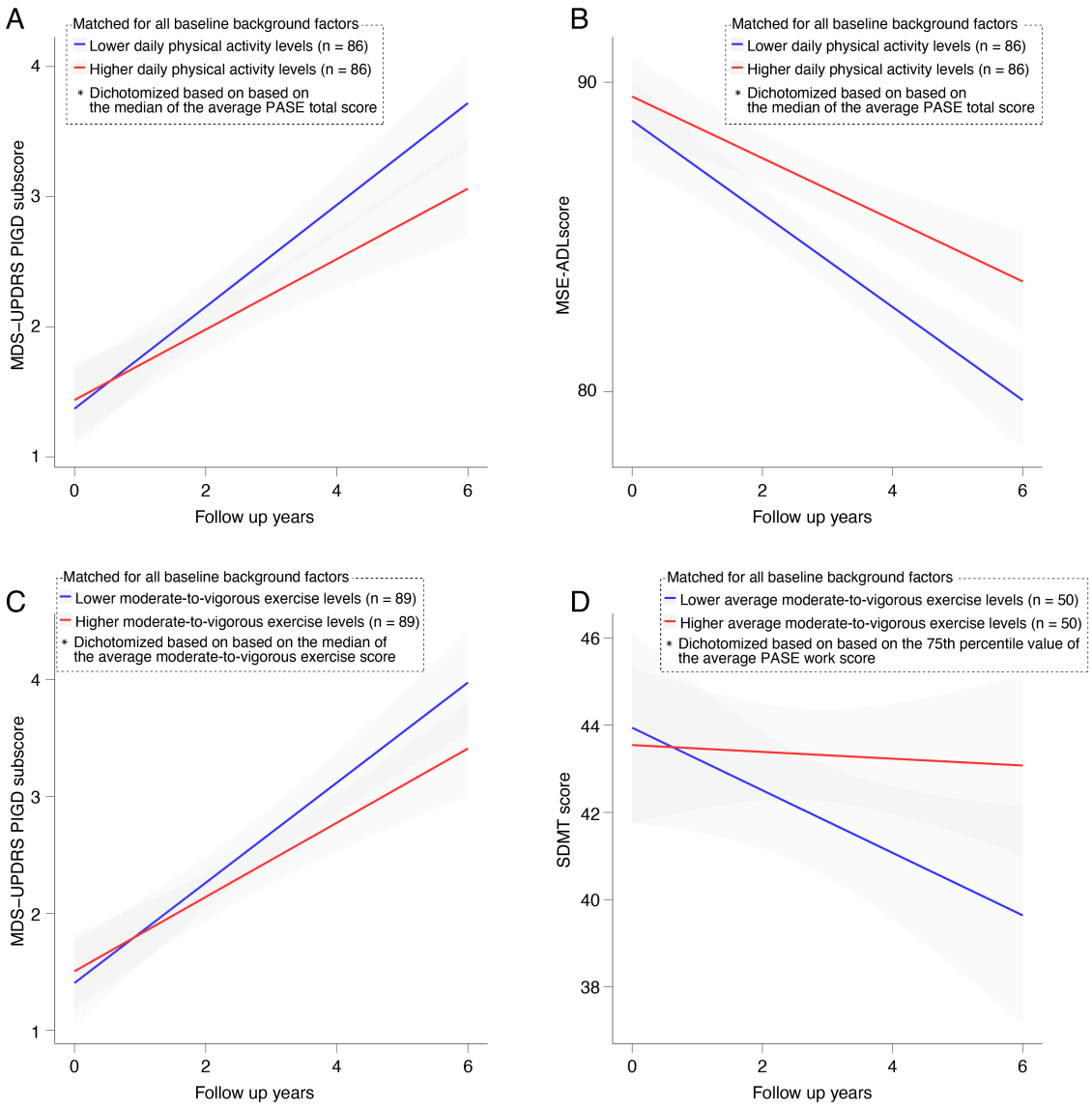

A
Matched for all baseline background factors
Lower daily physical activity levels (n = 86)
Higher daily physical activity levels (n = 86)
* Dichotomized based on based on the median of the average PASE total score
MDS–UPDRS PIGD subscore
Follow up years
B
Matched for all baseline background factors
Lower daily physical activity levels (n = 86)
Higher daily physical activity levels (n = 86)
* Dichotomized based on based on the median of the average PASE total score
MSE-ADLscore
Follow up years
C
Matched for all baseline background factors
Lower moderate-to-vigorous exercise levels (n = 89)
Higher moderate-to-vigorous exercise levels (n = 89)
* Dichotomized based on based on the median of the average moderate-to-vigorous exercise score
MDS–UPDRS PIGD subscore
Follow up years
D
Matched for all baseline background factors
Lower average moderate-to-vigorous exercise levels (n = 50)
Higher average moderate-to-vigorous exercise levels (n = 50)
* Dichotomized based on based on the 75th percentile value of the average PASE work score
SDMT score
Follow up years

Figure 4

TABLES

Table 1. Baseline characteristics of the enrolled subjects

	PD, N = 237[1]	**Control**, N = 158[1]	***P* value**[2]
Age (years)	63.0 (56.0–70.0)	64.0 (58.0–71.0)	0.51
Sex, Female	73.0 (30.8%)	60.0 (38.0%)	0.14
Disease duration (years)	3.0 (3.0–5.0)	–	
Hoen-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, meet (%)	105.0 (44.3%)	71.0 (44.9%)	0.90
Off MDS-UPDRS part3 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 (number)	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 (number)	0	1	
SCOPA-AUT total score	13.0 (7.0–20.0)	7.0 (4.0–13.0)	<0.001*
Missing (number)	1	0	
GDS-15 total score	5.0 (5.0–6.0)	5.0 (5.0–5.0)	0.024
Missing (number)	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 (number)	1	145	

[1] Data are expressed as median (interquartile range) or number (percentage). [2] *P* values were obtained by Wilcoxon rank sum test or Pearson's Chi-squared test, as appropriate. Since there were 24 comparison items, the value of 0.05 divided by 24 was used to determine statistical significance, and statistically significant items were marked with asterisks.

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

Table 2. Temporal change in clinical parameters of Parkinson's disease (PD) patients

	Follow-up years					
	1, N = 223[1]	**2**, N = 226[1]	**3**, N = 209[1]	**4**, N = 191[1]	**5**, N = 153[1]	**6**, N = 118[1]
Age (years)	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)
Sex, Female	71.0 (31.8%)	73.0 (32.3%)	65.0 (31.1%)	56.0 (29.3%)	46.0 (30.1%)	33.0 (28.0%)
Disease duration (years)	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)
Hoen-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 (number)	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, meet (%)	86.0 (38.6%)	93.0 (41.2%)	78.0 (37.3%)	75.0 (39.3%)	53.0 (34.6%)	42.0 (35.6%)
Off MDS-UPDRS part3 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 (number)	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 (number)	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 (number)	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 (number)	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 (number)	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 (number)	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 (number)	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 (number)	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 (number)	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 (number)	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 (number)	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 (number)	0	2	0	1	0	0
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 (number)	0	1	0	2	0	0

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

Table 3. Baseline clinical characteristics of propensity score-matched groups of Parkinson' disease (PD) patients

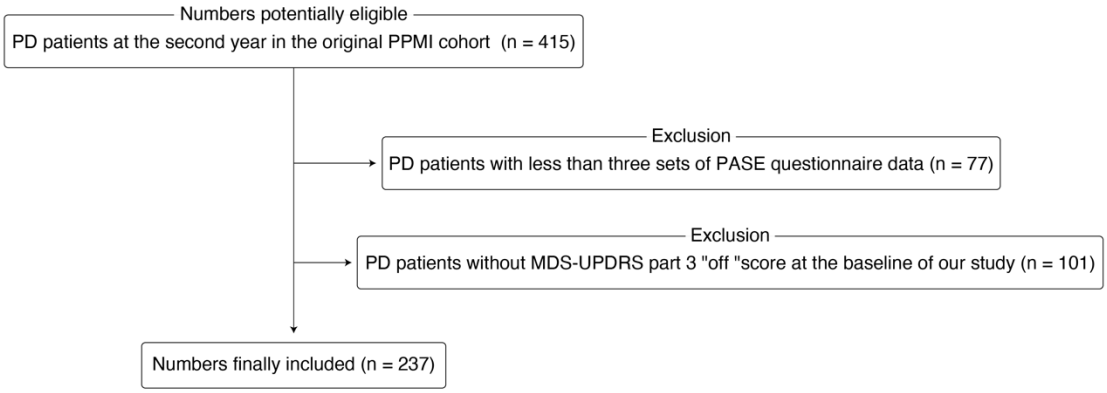
	Lower average overall regular physical activity, N = 86[1]	Higher average overall regular physical activity, N = 86[1]	*P* value[2]	SMD
Age (years)	64.5 (59.2–70.0)	63.0 (57.0–70.0)	0.59	0.075
Sex, Female	26.0 (30.2%)	26.0 (30.2%)	>0.99	<0.001
Disease duration (years)	3.5 (3.0–4.8)	3.0 (2.2–5.0)	0.92	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 part3 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-ADLscore	90.0 (90.0–90.0)	90.0 (85.0–95.0)	0.52	0.058

[1] Data are expressed as median (interquartile range) or number (percentage). [2] *P* values were obtained by Wilcoxon rank sum test or Pearson's Chi-squared test, as appropriate.

Abbreviations: SMD, standardized mean difference; MDS-UPDRS, Movement Disorders Society-sponsored revision of the Unified Parkinson's disease rating scale; PIGD, Postural Instability and Gait Disturbance; MOCA, Montreal Cognitive Assessment; HVLT-R, Hopkins Verbal Learning Test-Revised; JLO, Judgment of Line Orientation; LNS, Letter-Number Sequencing; SDMT, Symbol Digit Modalities Test; SCOPA-AUT, Scales for Outcomes in Parkinson's Disease-Autonomic; GDS-, 15-items version of Geriatric Depression Scale; ESS, Epworth Sleepiness Scale; RBDSQ, REM sleep Behavior Disorder Screening Questionnaire; MSE-ADL, Modified Schwab & England Activities of Daily Living scale.

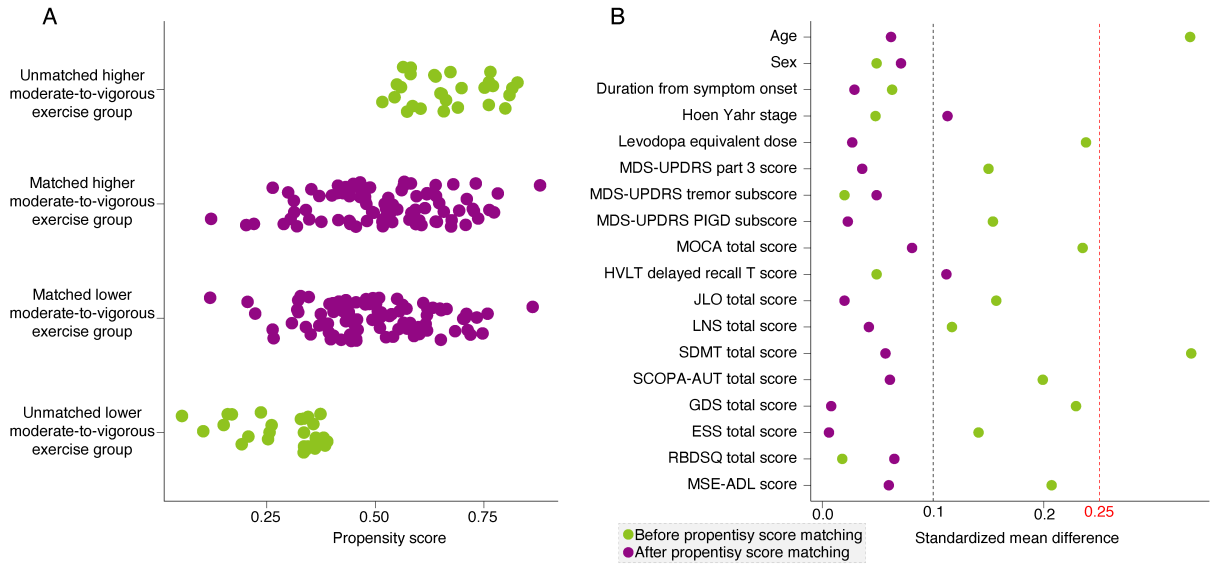
Supplementary figure titles and legends

eFigure 1. Study flowchart



Abbreviations: PPMI, Parkinson's Progression Markers Initiative; PD, Parkinson's disease; PASE, Physical Activity Scale for the Elderly; MDS-UPDRS, Movement Disorders Society-sponsored revision of the Unified Parkinson's disease rating scale.

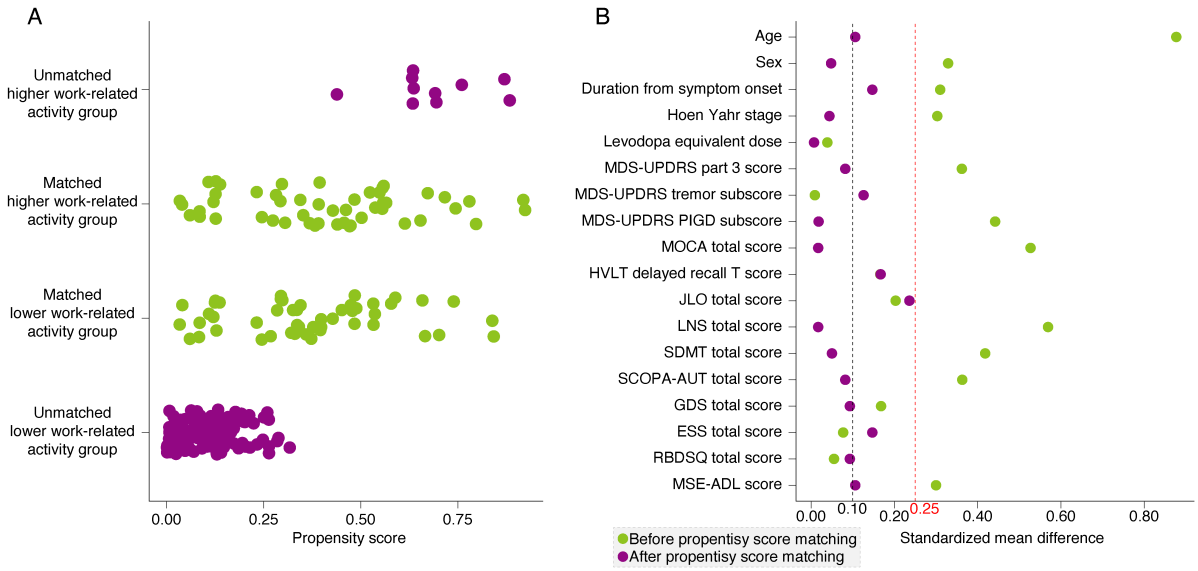
eFigure 2. Distribution of propensity scores and balance measures after propensity score matching for moderate-to-vigorous exercise levels



At first, Parkinson's disease (PD) patients were dichotomized using the median of the average moderate-to-vigorous exercise levels. After propensity score matching, higher and lower regular moderate-to-vigorous exercise groups both consisted of 89 PD patients (A) and were matched such that standardized mean differences between all background factors fell well within a modest cut-off of 0.25 (B).

Abbreviations: MDS-UPDRS, Movement Disorders Society-sponsored revision of the Unified Parkinson's disease rating scale; PIGD, Postural Instability and Gait Disturbance; MOCA, Montreal Cognitive Assessment; HVLT-R, Hopkins Verbal Learning Test-Revised; JLO, Judgment of Line Orientation; LNS, Letter-Number Sequencing; SDMT, Symbol Digit Modalities Test; SCOPA-AUT, Scales for Outcomes in Parkinson's Disease-Autonomic; GDS, Geriatric Depression Scale; ESS, Epworth Sleepiness Scale; RBDSQ, REM sleep Behavior Disorder Screening Questionnaire; MSE-ADL, Modified Schwab & England Activities of Daily Living scale.

eFigure 3. Distribution of propensity scores and balance measures after propensity score matching for work-related activity levels



At first, Parkinson's disease (PD) patients were dichotomized using the 75th percentile value of the average Physical Activity Scale for the Elderly work score. After propensity score matching, higher and lower regular physical activity groups both consisted of 50 PD patients (A) and were matched such that standardized mean differences between all background factors fell within a modest cut-off of 0.25 (B).

Abbreviations: MDS-UPDRS, Movement Disorders Society-sponsored revision of the Unified Parkinson's disease rating scale; PIGD, Postural Instability and Gait Disturbance; MOCA, Montreal Cognitive Assessment; HVLT-R, Hopkins Verbal Learning Test-Revised; JLO, Judgment of Line Orientation; LNS, Letter-Number Sequencing; SDMT, Symbol Digit Modalities Test; SCOPA-AUT, Scales for Outcomes in Parkinson's Disease-Autonomic; GDS, Geriatric Depression Scale; ESS, Epworth Sleepiness Scale; RBDSQ, REM sleep Behavior Disorder Screening Questionnaire; MSE-ADL, Modified Schwab & England Activities of Daily Living scale.

Supplementary TABLES

eTable 1. Baseline characteristics for Parkinson's disease (PD) patients with 5 years or less of follow-up or 6 years of follow-up

	Follow up for 5 years or less, N = 119[1]	**Follow up for 6 years**, N = 118[1]	***P* value**[2]
Baseline dates	2014/06/30 (2014/02/28–2014/12/16)	2013/07/31 (2013/05/31–2013/11/30)	<0.001*
Age (years)	64.0 (56.0, 72.0)	63.0 (56.0, 69.0)	0.22
Sex, Female	40 (34%)	33 (28%)	0.35
Disease duration (years)	4.0 (3.0, 5.0)	3.0 (2.0, 4.0)	0.025
Hoen-Yahr stage	2.0 (1.5, 2.0)	2.0 (1.0, 2.0)	0.42
Levodopa equivalent dose (mg)	100.0 (0.0, 300.0)	100.0 (0.0, 236.2)	0.54
PASE leisure score	48.1 (18.4, 107.6)	50.4 (17.8, 77.0)	0.49
PASE household score	85.0 (50.0, 121.0)	86.0 (51.2, 116.0)	0.73
PASE work score	0.0 (0.0, 24.0)	0.0 (0.0, 60.0)	0.92
PASE total score	183.1 (110.4, 257.2)	162.6 (111.5, 249.4)	0.81
PASE score of moderate-to-vigorous exercise	0.2 (0.0, 0.8)	0.1 (0.0, 0.8)	0.89
AAN quality metrics, meet (%)	53 (45%)	52 (44%)	0.94
Off MDS-UPDRS part3 score	25.0 (18.0, 34.0)	26.0 (19.0, 33.8)	0.89
Off MDS-UPDRS tremor subscore	5.0 (2.5, 9.0)	7.0 (4.0, 10.0)	0.035
Off MDS-UPDRS PIGD subscore	1.0 (1.0, 2.0)	1.0 (1.0, 2.0)	0.65
MOCA total score	27.0 (24.0, 29.0)	27.0 (25.0, 28.0)	0.92
HVLT-R delayed recall T score	44.0 (36.0, 53.0)	47.0 (38.0, 55.0)	0.11
JLO total score	26.0 (22.0, 28.0)	28.0 (24.0, 28.0)	0.20
Missing (number)	1	0	
LNS total score	11.0 (9.0, 12.0)	11.0 (9.0, 12.0)	0.71
SDMT total score	42.0 (35.0, 48.0)	42.0 (35.0, 48.0)	0.95
SCOPA-AUT total score	13.0 (7.0, 19.8)	13.0 (9.0, 20.0)	0.67
Missing (number)	1	0	
GDS-15 total score	5.0 (5.0, 6.0)	5.0 (5.0, 6.0)	0.53
Missing (number)	1	0	
ESS total score	6.0 (4.0, 10.0)	5.5 (4.0, 7.0)	0.24
RBDSQ total score	5.0 (3.0, 7.0)	5.0 (3.0, 7.0)	0.88
MSE-ADL score	90.0 (86.2, 95.0)	90.0 (81.2, 90.0)	0.10
Missing (number)	1	0	

[1] Data are expressed as median (interquartile range) or number (percentage). [2] *P* values were obtained by Wilcoxon rank sum test or Pearson's Chi-squared test, as appropriate. Since there were 25 comparison items, the value of 0.05 divided by 25 was used to determine statistical significance, and statistically significant items were marked with asterisks.

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

eTable 2. Sensitivity analyses using the multiple imputation methods

	Original			Multiple imputation method		
	Estimates	Bootstrap 95%CI, low	Bootstrap 95%CI, high	Estimates[1]	Bootstrap 95%CI, low[1]	Bootstrap 95%CI, high[1]
vs. PASE total score						
Off MDS-UPDRS part3 score	-0.018	-0.056	0.016	-0.025 (-0.026, -0.024)	-0.062 (-0.063, -0.061)	0.012 (0.010, 0.013)
Off MDS-UPDRS tremor subscore	-0.009	-0.045	0.026	-0.011 (-0.013, -0.010)	-0.050 (-0.051, -0.048)	0.027 (0.026, 0.029)
Off MDS-UPDRS PIGD subscore	-0.095	-0.135	-0.059	-0.098 (-0.099, -0.097)	-0.136 (-0.137, -0.135)	-0.061 (-0.062, -0.060)
MOCA total score	0.044	0.012	0.077	0.046 (0.045, 0.046)	0.012 (0.012, 0.013)	0.079 (0.078, 0.079)
HVLT-R delayed recall T score	-0.006	-0.046	0.030	-0.005 (-0.006, -0.005)	-0.044 (-0.045, -0.044)	0.034 (0.033, 0.034)
JLO total score	0.032	-0.003	0.070	0.031 (0.030, 0.031)	-0.007 (-0.007, -0.006)	0.067 (0.067, 0.068)
LNS total score	0.044	0.014	0.076	0.045 (0.044, 0.045)	0.013 (0.013, 0.013)	0.077 (0.076, 0.077)
SDMT total score	0.052	0.025	0.080	0.050 (0.050, 0.050)	0.022 (0.022, 0.023)	0.078 (0.077, 0.078)
SCOPA-AUT total score	-0.020	-0.049	0.012	-0.019 (-0.019, -0.019)	-0.050 (-0.051, -0.050)	0.012 (0.012, 0.013)
GDS-15 total score	-0.023	-0.070	0.017	-0.023 (-0.023, -0.023)	-0.066 (-0.067, -0.066)	0.021 (0.020, 0.021)
ESS total score	-0.009	-0.042	0.026	-0.008 (-0.009, -0.008)	-0.042 (-0.042, -0.042)	0.025 (0.025, 0.025)
RBDSQ total score	-0.015	-0.049	0.021	-0.015 (-0.015, -0.015)	-0.048 (-0.048, -0.047)	0.018 (0.018, 0.018)
MSE-ADL score	0.077	0.042	0.115	0.077 (0.077, 0.077)	0.039 (0.039, 0.039)	0.114 (0.114, 0.115)
vs. PASE leisure score						
Off MDS-UPDRS part3 score	-0.017	-0.051	0.018	-0.022 (-0.023, -0.021)	-0.059 (-0.060, -0.058)	0.015 (0.014, 0.017)
Off MDS-UPDRS tremor subscore	0.002	-0.032	0.029	0.000 (-0.002, 0.001)	-0.039 (-0.040, -0.037)	0.038 (0.037, 0.040)
Off MDS-UPDRS PIGD subscore	-0.073	-0.112	-0.037	-0.071 (-0.072, -0.070)	-0.109 (-0.110, -0.108)	-0.033 (-0.034, -0.032)
MOCA total score	0.042	0.009	0.075	0.042 (0.041, 0.042)	0.009 (0.008, 0.009)	0.075 (0.075, 0.076)
HVLT-R delayed recall T score	-0.026	-0.066	0.020	-0.023 (-0.024, -0.023)	-0.063 (-0.063, -0.062)	0.016 (0.016, 0.017)
JLO total score	0.028	-0.010	0.063	0.027 (0.026, 0.027)	-0.010 (-0.011, -0.010)	0.064 (0.063, 0.065)
LNS total score	0.036	0.002	0.068	0.037 (0.036, 0.037)	0.005 (0.005, 0.006)	0.069 (0.068, 0.069)
SDMT total score	0.006	-0.021	0.035	0.003 (0.003, 0.004)	-0.025 (-0.025, -0.024)	0.032 (0.031, 0.032)
SCOPA-AUT total score	-0.014	-0.043	0.017	-0.014 (-0.014, -0.013)	-0.045 (-0.045, -0.045)	0.018 (0.018, 0.018)
GDS-15 total score	-0.027	-0.073	0.020	-0.027 (-0.027, -0.027)	-0.071 (-0.071, -0.071)	0.017 (0.016, 0.017)
ESS total score	-0.033	-0.067	0.001	-0.033 (-0.033, -0.033)	-0.066 (-0.067, -0.066)	0.001 (0.000, 0.001)
RBDSQ total score	0.006	-0.030	0.038	0.006 (0.006, 0.006)	-0.028 (-0.028, -0.027)	0.039 (0.038, 0.039)
MSE-ADL score	0.040	0.005	0.079	0.040 (0.040, 0.040)	0.002 (0.002, 0.003)	0.078 (0.078, 0.079)
vs. PASE household score						
Off MDS-UPDRS part3 score	-0.019	-0.052	0.015	-0.020 (-0.022, -0.019)	-0.057 (-0.059, -0.056)	0.016 (0.014, 0.017)
Off MDS-UPDRS tremor subscore	-0.006	-0.043	0.030	-0.003 (-0.005, -0.001)	-0.041 (-0.043, -0.039)	0.035 (0.033, 0.037)
Off MDS-UPDRS PIGD subscore	-0.078	-0.113	-0.041	-0.080 (-0.082, -0.079)	-0.117 (-0.119, -0.116)	-0.044 (-0.045, -0.042)
MOCA total score	0.029	0.006	0.061	0.032 (0.032, 0.033)	-0.001 (-0.001, -0.001)	0.065 (0.064, 0.065)
HVLT-R delayed recall T score	0.016	-0.019	0.052	0.019 (0.019, 0.020)	-0.019 (-0.020, -0.019)	0.058 (0.057, 0.058)
JLO total score	0.014	-0.023	0.051	0.014 (0.014, 0.015)	-0.022 (-0.023, -0.022)	0.050 (0.050, 0.051)
LNS total score	0.050	0.017	0.080	0.052 (0.051, 0.052)	0.021 (0.020, 0.021)	0.083 (0.082, 0.083)
SDMT total score	0.039	0.012	0.070	0.039 (0.039, 0.040)	0.012 (0.011, 0.012)	0.067 (0.067, 0.067)
SCOPA-AUT total score	-0.026	-0.059	0.068	-0.026 (-0.026, -0.026)	-0.056 (-0.057, -0.056)	0.005 (0.005, 0.006)
GDS-15 total score	0.005	-0.040	0.049	0.005 (0.004, 0.005)	-0.038 (-0.038, -0.037)	0.048 (0.047, 0.048)
ESS total score	-0.007	-0.040	0.024	-0.007 (-0.007, -0.007)	-0.040 (-0.040, -0.040)	0.026 (0.026, 0.026)
RBDSQ total score	0.002	-0.030	0.035	0.002 (0.002, 0.002)	-0.030 (-0.030, -0.030)	0.034 (0.034, 0.035)
MSE-ADL score	0.088	0.050	0.123	0.087 (0.087, 0.087)	0.051 (0.050, 0.051)	0.124 (0.124, 0.124)
vs. PASE work score						
Off MDS-UPDRS part3 score	-0.002	-0.040	0.033	-0.008 (-0.009, -0.007)	-0.045 (-0.046, -0.044)	0.029 (0.028, 0.030)
Off MDS-UPDRS tremor subscore	-0.016	-0.051	0.022	-0.021 (-0.022, -0.020)	-0.059 (-0.060, -0.058)	0.018 (0.017, 0.019)
Off MDS-UPDRS PIGD subscore	-0.046	-0.084	-0.008	-0.049 (-0.051, -0.048)	-0.087 (-0.088, -0.086)	-0.011 (-0.012, -0.010)
MOCA total score	0.018	-0.014	0.052	0.018 (0.017, 0.018)	-0.015 (-0.016, -0.015)	0.051 (0.050, 0.051)
HVLT-R delayed recall T score	-0.001	-0.038	0.039	-0.002 (-0.003, -0.002)	-0.042 (-0.041, -0.042)	0.036 (0.036, 0.037)
JLO total score	0.023	-0.017	0.059	0.020 (0.020, 0.021)	-0.017 (-0.017, -0.016)	0.057 (0.057, 0.058)
LNS total score	0.006	-0.025	0.039	0.004 (0.004, 0.005)	-0.027 (-0.028, -0.027)	0.036 (0.036, 0.037)
SDMT total score	0.066	0.037	0.093	0.064 (0.064, 0.064)	0.036 (0.036, 0.037)	0.092 (0.091, 0.092)
SCOPA-AUT total score	-0.000	-0.033	0.031	-0.000 (-0.000, 0.000)	-0.031 (-0.032, -0.031)	0.031 (0.031, 0.032)
GDS-15 total score	-0.020	-0.064	0.029	-0.020 (-0.021, -0.020)	-0.064 (-0.064, -0.063)	0.023 (0.023, 0.024)
ESS total score	0.026	-0.006	0.060	0.026 (0.026, 0.027)	-0.007 (-0.007, -0.006)	0.060 (0.059, 0.060)
RBDSQ total score	-0.040	-0.070	-0.007	-0.039 (-0.039, -0.039)	-0.072 (-0.072, -0.072)	-0.007 (-0.007, -0.006)
MSE-ADL score	0.034	-0.003	0.072	0.034 (0.034, 0.034)	-0.004 (-0.004, -0.003)	0.072 (0.072, 0.072)
vs. Moderate-to-vigorous exercise						
Off MDS-UPDRS part3 score	-0.009	-0.049	0.029	-0.011 (-0.013, -0.010)	-0.0590 (-0.052, -0.048)	0.027 (0.025, 0.029)
Off MDS-UPDRS tremor subscore	-0.003	-0.043	0.031	-0.009 (-0.011, -0.007)	-0.049 (-0.051, -0.047)	0.031 (0.029, 0.034)
Off MDS-UPDRS PIGD subscore	-0.088	-0.129	-0.048	-0.077 (-0.079, -0.075)	-0.116 (-0.118, -0.114)	-0.038 (-0.039, -0.036)
MOCA total score	0.051	0.015	0.086	0.047 (0.046, 0.047)	0.012 (0.011, 0.013)	0.081 (0.080, 0.082)
HVLT-R delayed recall T score	-0.025	-0.066	0.016	-0.023 (-0.024, -0.022)	-0.064 (-0.065, -0.063)	0.017 (0.016, 0.018)
JLO total score	0.046	0.009	0.085	0.043 (0.042, 0.044)	0.005 (0.004, 0.006)	0.082 (0.080, 0.083)
LNS total score	0.043	0.008	0.078	0.042 (0.041, 0.043)	0.009 (0.008, 0.010)	0.075 (0.074, 0.076)
SDMT total score	0.014	-0.016	0.045	0.011 (0.010, 0.011)	-0.019 (-0.020, -0.018)	0.040 (0.039, 0.040)
SCOPA-AUT total score	-0.004	-0.036	0.032	-0.004 (-0.004, -0.003)	-0.036 (-0.036, -0.036)	0.029 (0.029, 0.029)
GDS-15 total score	-0.010	-0.054	0.035	-0.010 (-0.010, -0.009)	-0.055 (-0.055, -0.054)	0.035 (0.035, 0.036)
ESS total score	-0.032	-0.066	0.003	-0.034 (-0.034, -0.033)	-0.068 (-0.069, -0.068)	0.001 (0.001, 0.002)
RBDSQ total score	-0.006	-0.041	0.027	-0.007 (-0.007, -0.007)	-0.041 (-0.041, -0.041)	0.027 (0.027, 0.027)
MSE-ADL score	0.051	0.012	0.087	0.052 (0.051, 0.052)	0.013 (0.012, 0.013)	0.091 (0.091, 0.092)

[1] Data are expressed as mean (95%CIs).

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

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	#1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	#1
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	#3, #4
Objectives	3	State specific objectives, including any prespecified hypotheses	#4
Methods			
Study design	4	Present key elements of study design early in the paper	#5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	#5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	#5
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	#8, #11, figure3
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	#7, #8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	#6, #7
Bias	9	Describe any efforts to address potential sources of bias	#7,#8
Study size	10	Explain how the study size was arrived at	N.A
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	#8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	#7, #8
		(*b*) Describe any methods used to examine subgroups and interactions	#7, #8
		(*c*) Explain how missing data were addressed	#8
		(*d*) If applicable, explain how loss to follow-up was addressed	#9, #10, table e-1
		(*e*) Describe any sensitivity analyses	#8
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	#9, figure e-1
		(b) Give reasons for non-participation at each stage	figure e-1
		(c) Consider use of a flow diagram	figure e-1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	#9, table 1
		(b) Indicate number of participants with missing data for each variable of interest	table e-1
		(c) Summarise follow-up time (eg, average and total amount)	#5, #9, table 2
Outcome data	15*	Report numbers of outcome events or summary measures over time	#10, figure 1–2
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	#10, table e-2
		(*b*) Report category boundaries when continuous variables were categorized	N.A.
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N.A.
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	#11, figure 3–4, table 3 figure e-2–e-3, table e-2
Discussion			
Key results	18	Summarise key results with reference to study objectives	#12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	#14
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	#12, #13, #14
Generalisability	21	Discuss the generalisability (external validity) of the study results	#12, #13
Other information			

Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Title page

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.