Movement Disorders
CLINICAL PRACTICE

BRIEF REPORT

Effect of Exercise and Rehabilitation Therapy on Risk of Hospitalization in Parkinson's Disease

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ABSTRACT: Background: Exercise and physical therapy (PT) can improve motor function and quality of life in individuals with Parkinson's disease (PD), but their role in hospitalization avoidance is not well-studied.
Objectives: To determine the longitudinal and temporal association of exercise and PT use with hospital encounter.
Methods: Longitudinal regression and χ^2 analyses were performed on Parkinson's Foundation Parkinson's Outcome Project exercise and PT use data from 4674 and 9259 persons with PD, respectively.
Results: Greater exercise duration and intensity were associated with reduced odds of hospital encounter, whereas both PT and occupational therapy use were associated with increased odds. In the 2 years before a hospital encounter, there was an increased frequency of PT use, but not reductions in exercise.
Conclusions: Consistent exercise may reduce hospitalization risk whereas PT referral may identify at-risk individuals without preventing this outcome. Further work to incentivize consistent exercise in PD may reduce healthcare use.

Individuals with Parkinson's disease (PD) have 1.4 times more hospital admissions than age-matched peers and lengths of stay that are 1.19 times longer.[1] Hospitalizations for individuals with PD are more likely a result of reduced mobility, falls, trauma, infections, and psychosis,[2] so exercise-based or physical therapy (PT) and occupational therapy (OT) interventions that affect mobility, falls, and trauma could have a substantial effect on hospital encounter rates. Risk factors for a prior hospital encounter include use of PT and increased time on the standardized Timed Get Up and Go (TUG) test,[2] among others, but reverse causality could also explain this finding if hospital encounter increases PT/OT use or reduces TUG time. Therefore, our goal was to evaluate more closely the temporal relationship between exercise duration/intensity, PT use, and hospital encounters to better understand the preventative capacity of these interventions for emergency room (ER) visits or hospital admissions. In this study, we use data from the Parkinson's Foundation (PF) Parkinson's Outcome Project (POP) longitudinal study cohort with over 13,000 subjects and 35,000 study visits to determine whether increased exercise duration or intensity and use of PT/OT is associated with reduced risk of hospital encounter at a subsequent encounter. Additionally, we assessed whether reductions in exercise patterns or a PT referral were associated with a hospital encounter in close temporal proximity.

Methods

Data and Participants

Data from this study were obtained between April 4, 2009 and September 14, 2020 including only individuals with more than one study visit from the PF-POP, which is a multicenter, international prospective observational cohort study to assess clinical

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care practices and outcomes.[3] The study has enrolled individuals with PD followed at PF Centers of Excellence (COE). Inclusion and exclusion criteria are described in prior reports.[3] Informed consent was obtained from each participant and each individual COE's Institutional Review Board approved data collection for use in de-identified data analyses. The POP collects data at yearly visits, including demographics, disease duration, Hoehn and Yahr (H&Y) stage, medical and family history, brief neuropsychological and cognitive tests, medication use, PT/OT use, and self-reported quality of life measures. Functional mobility is assessed using the TUG test with longer times indicating worse performance.[4] Patient-reported exercise duration is in hours per week and exercise intensity (low, moderate, and high) was self-reported based on examples of activities that generate different levels of metabolic equivalents. Hospital encounter, defined as the combined endpoint of either ER visit or hospital admission, are self-reported by participants and classified into categories: behavior, deep brain stimulation, gastrointestinal, infection, injury, surgery, and other.

Statistical Analysis

R software was used for the described statistical analyses (R Foundation, Vienna, Austria). Observations with missing data from analyses were excluded. Demographic and clinical variables were compared between those with or without a hospital encounter using χ^2 tests for categorical variables and two-tailed t tests for continuous variables. To determine the longitudinal association between hospital encounter and exercise or PT/OT use, generalized linear mixed effects longitudinal regression models with random intercepts and random slopes were used with the outcome of hospital encounter, a composite outcome of ER visit or hospital admission, and primary predictor variables of (1) exercise duration, (2) exercise intensity-weighted duration, (3) PT use, and (4) OT use, adjusting for disease stage, mobility (TUG), age, and cognition z score at baseline as potential confounders. χ^2 testing was used to compare proportion of blocks of two study visit periods, typically a year (mean = 1.34 years with standard deviation [SD] = 0.69) between visits, with exercise reduction or PT referral before a visit in study visit blocks immediately preceding or not preceding a visit with a reported hospital encounter. Numbers of individuals or observations for various analyses are indicated in the text.

Age and TUG time were standardized based on the mean and SD values at the baseline visit. Exercise duration was expressed as hours of moderate- or high-intensity exercise per week and standardized using the mean and SD of all observations. An exercise intensity-weighted duration was calculated using the modified Godin model, which has been validated in other conditions as a measure of moderate-vigorous intensity exercise that provides a bonus for vigorous exercise participation.[5,6] We multiplied the number of hours of light, moderate, and vigorous exercise by the number of metabolic equivalents (METs) associated with that exercise intensity: three, five, and nine, respectively. For exercise duration, light exercise was excluded to improve sensitivity and reduce variability because specifically higher intensity exercise has shown to be beneficial in PD.[5–9]

Data Sharing

The data that support the findings of this study are available on request from the PF. Restrictions apply to the availability of these data, which were used under data use agreement for this study. Each COE's institutional review board approved the data collections, and informed consent was obtained from each participant.

Results

Population Characteristics

We included 7010 individuals with PD for the model containing total exercise hours, 4674 individuals with PD for the model containing exercise intensity, and 9259 individuals for the model with PT use as a predictor. Individuals with a hospital encounter were more likely female (37.8% vs. 35.8%, $P = 0.02$), a higher H&Y stage ($P < 0.0001$), having a higher number of baseline comorbidities ($P < 0.0001$), not living at home ($P < 0.001$), having a care partner ($P < 0.0001$), taking levodopa ($P < 0.0001$), having deep brain stimulation ($P < 0.0001$), using PT ($P < 0.0001$), using OT ($P < 0.0001$), using speech therapy ($P < 0.0001$), using mental health therapies, older at baseline ($P < 0.0001$), younger age at PD onset ($P < 0.0001$), longer duration of PD disease ($P < 0.0001$), lower cognition score ($P < 0.0001$), worse Parkinson's Disease Questionnaire (PDQ)-39 ($P < 0.0001$), and greater TUG duration ($P < 0.0001$) (Table 1). Among individuals with or without hospital encounter, there were no differences in race, number of medications at baseline, and type of care partner (Table 1). Reasons for hospital encounter included injury (n = 1281, 20%), surgery (n = 650, 10.2%), infection (n = 483, 7.6%), deep brain stimulation (n = 417, 6.5%), gastrointestinal (n = 204, 3.2%), behavior (n = 136, 2.1%), and other (n = 3220, 50.4%). In this cohort, the average yearly rates of hospital admission, ER visit, or hospital encounter were 0.327 (SD = 0.792), 0.408 (SD = 0.765), and 0.734 (SD = 1.29), respectively.

Exercise Is Associated with Reduced Odds Whereas PT/OT Use Is Associated with Increased Odds of Hospital Encounter

Using generalized linear mixed effects longitudinal regression models, we tested the hypotheses that exercise duration, exercise intensity, PT use, and OT use were protective against hospital encounter. When accounting for confounding because of age, H&Y stage, baseline mobility with TUG testing, and cognition,

TABLE 1 Baseline characteristics of individuals with or without any hospital encounter

Variable	Levels	Individuals without any hospital encounter (n = 5314) n (%)	Individuals with any hospital encounter (n = 7005) n (%)	*P* value*
Sex	Female	1901 (35.8)	2649 (37.8)	0.021
	Male	3413 (64.2)	4356 (62.2)	
Race	White	4969 (94.5)	6608 (94.9)	0.130
	Black	95 (1.8)	97 (1.4)	
	Pacific Islander	12 (0.2)	12 (0.2)	
	Asian	129 (2.5)	148 (2.1)	
	American Indian	24 (0.5)	49 (0.7)	
	Multiple races	31 (0.6)	46 (0.7)	
H&Y stage	0–2	3679 (73.9)	4110 (62.8)	2.03e−35
	2.5–3	1038 (20.8)	1890 (28.9)	
	4–5	264 (5.3)	544 (8.3)	
No. of medications	1	584 (36.8)	475 (34.3)	0.152
	2	613 (38.6)	514 (37.1)	
	≥3	390 (24.6)	395 (28.5)	
No. of comorbidities	1	1460 (45.4)	2084 (50)	5.74e−09
	2	680 (21.1)	893 (21.4)	
	≥3	1077 (33.5)	1193 (28.7)	
Living situation	At home	2065 (98)	1750 (96.4)	1.90e−04
	Skilled care	22 (1)	51 (2.8)	
	Other	21 (1)	14 (0.8)	
Care partner	No	1081 (20.3)	1126 (16.1)	9.94e−10
	Yes	4235 (79.7)	5886 (83.9)	
Type of care partner	Spouse/partner	3957 (93.2)	5412 (91.8)	0.058
	Other relative	172 (4.1)	278 (4.7)	
	Paid caregiver	95 (2.2)	164 (2.8)	
	Other	21 (0.5)	41 (0.7)	
Levodopa	No	350 (17.2)	172 (9.8)	5.34e−11
	Yes	1682 (82.8)	1583 (90.2)	
LEDD	Mean ± SD	243 ± 420	199 ± 532	2.46e−07
	Min, max	0, 6100	0, 21,441	
Deep brain stimulation	No	261 (97.8)	574 (81.7)	1.92e−10
	Yes	6 (2.2)	129 (18.3)	
Physical therapy use	No	3647 (68.8)	4056 (57.9)	2.20e−35
	Yes	1651 (31.2)	2951 (42.1)	

(Continues)

TABLE 1 *Continued*

Variable	Levels	Individuals without any hospital encounter (n = 5314) n (%)	Individuals with any hospital encounter (n = 7005) n (%)	*P* value*
Occupational therapy use	No	4864 (92)	6011 (85.7)	1.64e−26
	Yes	425 (8)	1000 (14.3)	
Visits with reported PT use and moderate or high-intensity exercise	Both moderate or high-intensity exercise and PT use	1531 (22.77)	1092 (27.04)	<2.2e−16
	Only moderate or high-intensity exercise	2363 (35.14)	889 (22.01)	
	Only PT use	983 (14.62)	1075 (26.62)	
	Neither moderate or high-intensity exercise or PT use	1848 (27.48)	983 (24.34)	
Speech communication therapy use	No	1892 (91.1)	1569 (87)	4.69e−05
	Yes	184 (8.9)	234 (13)	
Swallowing therapy use	No	2004 (96.7)	1695 (94.1)	1.37e−04
	Yes	69 (3.3)	107 (5.9)	
Psychology use	No	1983 (95.8)	1664 (92.5)	2.62e−05
	Yes	88 (4.2)	134 (7.5)	
Psychiatry use	No	1943 (93.8)	1620 (90)	2.02e−05
	Yes	129 (6.2)	180 (10)	
Age	Mean ± SD	66.78 ± 9.93	67.9 ± 9.55	<2.2e−16
	Min, max	27, 95	25, 95	
Age at PD onset	Mean ± SD	59.09 ± 10.98	58.57 ± 11.32	<2.2e−16
	Min, max	15, 90	7, 91	
PD duration	Mean ± SD	7.67 ± 5.8	9.31 ± 6.42	<2.2e−16
	Min, max	0, 59	0, 54	
Cognition *z* score	Mean ± SD	0.05 ± 0.77	−0.02 ± 0.74	<2.2e−16
	Min, max	−3.195, 16.7	−4.468, 2.005	
PDQ39	Mean ± SD	21.94 ± 15.23	25.93 ± 16.13	<2.2e−16
	Min, max	0, 83.3	0, 100	
TUG time (s)	Mean ± SD	12.26 ± 6.32	13.66 ± 7.41	<2.2e−16
	Min, max	0, 46	0, 66	

**P*-values from χ^2 test for categorical variables and *t* test for continuous variables.
Abbreviations: H&Y, Hoehn and Yahr; PD, Parkinson's disease; PDQ39, Parkinson's Disease Questionnaire 39; TUG, Timed Up and Go; LEDD, levodopa equivalent daily dosage.

both exercise duration (odds, 0.899; 95% CI, 0.847–0.953) and intensity (odds, 0.927; 95% CI, 0.874–0.983) were associated with reduced odds of hospital encounter (Table 2). The model for exercise duration included random intercepts, but not random slopes because it failed to converge with the latter. Older age and H&Y stage 2.5 to 3 (as compared with H&Y stages 0–2) were significantly associated with increased odds of hospital encounter in the models using exercise as a covariate. In these two models, there were 4674 subjects with 8074 observations. Both PT use (odds, 2.149; 95% CI, 2.022, 2.284) and OT use (odds, 2.866; 95% CI, 2.629, 3.124) were associated with increased odds of hospital encounter. All of the covariates in these two models were positively associated with increased odds of hospital encounter except for baseline cognition, where better cognition decreased odds of hospital encounter. In these two models, there were 9256 subjects and 26,927 observations. There was no significant interaction between H&Y stage and exercise, or PT/OT use in any of these models. Additionally, 18%, 32%, and 25% of study visits had reported only PT use, only moderate/high intensity exercise, or both, respectively, with similar age distribution among individuals (Table S1).

Reductions in Exercise But Not Occurrences of PT Referral Are Temporally Correlated with Hospital Encounter

Next, we tested the hypothesis that preceding a hospital encounter, there was more likely to be reduced exercise intensity, exercise duration, or lower incidence of PT referral. Blocks of three study visits were identified with either three consecutive visits without a hospital encounter (No-No-No [NNN]) or two consecutive visits without hospital encounter followed by a visit with reported preceding hospital encounter (No-No-Yes [NNY]). This strategy was used to remove potential confounding from changes in exercise or PT referral occurring during the same study period as a hospital encounter. At least two study visits before the visit when a hospital encounter is needed to calculate a change in exercise. Using χ^2 tests, we compared the frequency of exercise reduction between the first two visits or frequency of PT referral at the middle visit in NNN versus NNY blocks. Reductions in exercise duration ($\chi^2 = 1.510$, $P = 0.666$) or exercise intensity ($\chi^2 = 1.120$, $P = 1.00$) did not happen more frequently in NNY versus NNN blocks (Table S2). However, there was a significantly higher proportion of PT referrals at the middle visit in NNY blocks ($\chi^2 = 19.7$, $P = 0.002$) (Table S2). Of the individuals (n = 639) with a PT referral at the middle visit of a NNN or NNY block, age, H&Y stage, TUG test time, cognition *z* score, or exercise time were not associated with increased odds of a NNY block in a logistic regression model (Table 2).

Discussion

In this analysis of the POP data, we demonstrate that increased exercise duration and intensity correlate with reduced odds of hospital encounter using longitudinal data, when controlling for variables such as disease stage, age, and cognitive function that can affect both exercise and hospitalization. Given the multiple benefits of exercise in preclinical models and controlled trials, the association with reduced hospitalization is not surprising.[7,9–13] These benefits may occur through improvement in aerobic capacity, mitochondrial function, immunity, angiogenesis, and release of neurotrophic factors.[9,11–13] Furthermore, reductions in exercise duration or intensity within two study visit periods (~2 years) did not occur more frequently before an immediate subsequent hospital encounter. This finding suggests that the protective effects of exercise can be persistent even with short-term fluctuations in exercise. Recently, exercise has been shown to slow impairment in gait stability, activities of

TABLE 2 Longitudinal association of exercise or rehabilitation therapy with odds of hospital encounter

Co-variates	Exercise duration**			Exercise intensity			Physical therapy use			Occupational therapy use			Physical therapy referral at middle visit		
	OR	SE	*P* value	OR	SE	*P* value	OR	SE	*P* value	OR	SE	*P* value	OR	SE	*P* value
Follow-up time (y)	1.09	0.01	<0.001	1.09	0.01	<0.001	1.01	0.006	<0.001	1.09	0.006	<0.001			
Age*	1.14	0.034	<0.001	1.14	0.034	<0.001	1.12	0.02	<0.001	1.15	0.02	<0.001	1.26	0.146	0.114
H&Y 2.5–3	1.34	0.077	<0.001	1.35	0.077	<0.001	1.36	0.044	<0.001	1.41	0.044	<0.001	1.08	0.315	0.81
H&Y 4–5	1.27	0.237	0.307	1.28	0.237	0.301	1.41	0.1	<0.001	1.39	0.101	0.001	2.15	0.579	0.187
TUG time (s)*	1.06	0.043	0.167	1.07	0.043	0.145	1.14	0.021	<0.001	1.14	0.021	<0.001	1.08	0.069	0.246
Cognition *z* score	0.967	0.047	0.474	0.961	0.047	0.397	0.909	0.028	<0.001	0.936	0.028	0.02	1.2	0.209	0.382
Variable of interest	0.899	0.03	<0.001	0.927	0.03	0.012	2.15	0.031	<0.001	2.87	0.044	<0.001	0.84	0.146	0.241

*Age and TUG time were standardized based on the mean and SD values at the baseline visit.
**Exercise duration was standardized using the mean and SD of all observations.
Abbreviations: H&Y, Hoehn and Yahr; OR, odds ratio; SD, standard deviation; SE, standard error; TUG, Timed Up and Go.

daily living, and cognitive processing in early PD[12]. Exercise may reduce hospitalizations in PD through reduction in overall frailty, reducing falls, and improvement of medical comorbidities, which if promoted in a consistent way throughout multiple PD centers could reduce hospitalization rates.[14] Our findings suggest that exercise may be a potential strategy to reduce hospitalizations and therefore, cost of PD-related healthcare.[15,16]

Interestingly, consistent use of PT/OT is associated with increased odds of hospital encounter and PT referral was more likely to precede a study period with a subsequent hospital encounter (Table 2). This finding is consistent with other studies.[2] Several studies have shown benefit of targeted PT to improve function, which suggests that consistent PT use is a marker of individuals with mobility problems who are at risk for hospital encounter.[17–21] Because the POP data do not capture the specific modality or quantity of PT/OT used, it is possible that looking only at evidence-based PD-specific therapies may prevent hospital encounters in future studies. None of the analyzed covariates predicted hospital encounters among individuals who had a preceding recent PT referral, but PT referrals captured by the POP study may be reactive to falls, surgeries, or other illnesses unrelated to PD. Other limitations of these analyses include lack of granularity in types of hospital encounter, reliance on self-reported measures, inability to differentiate modalities of exercise or PT/OT, and its observational nature.

Further studies should look at whether various forms of exercise or PT are effective in reducing risk of specific reasons for hospital encounters. Exercise has multiple benefits in PD and now this study extends its role to reducing risk of hospital encounter. These data suggest that exercise incentive programs could be studied to reduce PD-related healthcare costs.[15,16]

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Author Roles

(1) Research project: A. Conception, B. Organization, C. Execution; (2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique; (3) Manuscript: A. Writing of the First Draft, B. Review and Critique.

G.T.K.: 1A, 1B, 1C, 2A, 2C, 3A, 3B
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S.L.: 2A, 2B, 2C, 3B
H.L.: 2B 2C, 3B
K.A.M.: 1A, 1B, 1C, 2A, 2C, 3B

Disclosures

Ethical Compliance Statement: Informed consent was obtained from each participant and each individual Parkinson's Foundation Center of Excellence's Institutional Review Board approved data collection for use in de-identified data analyses. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

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Supporting Information

Supporting information may be found in the online version of this article.

Table S1 Frequency of visits with moderate to high intensity exercise and/or physical therapy (PT) use with corresponding age distribution.

Table S2 Association between hospital encounter and reduced exercise intensity, exercise duration, or PT referral preceding a hospital encounter.