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Predictors of outcomes in exercisers with Parkinson disease: A two-year longitudinal cohort study

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Abstract.
BACKGROUND: Exercise may modify disease progression in persons with Parkinson disease (PD).
OBJECTIVE: The purpose of this longitudinal cohort study was to determine factors that predict motor, activity, and participation-based outcomes over two years in exercisers with PD.
METHODS: A convenience sample with idiopathic PD was included in the analysis [$n = 74$; mean age 66.7(8.4) years; male 54%; median months post diagnosis 69.0(76.0), median Hoehn and Yahr score 1.0(2.0)]. Exercise behaviors (minutes of exercise/week, peak rate of perceived exertion (RPE) and mode of exercise) and outcomes of impairment [grip strength], activity [10-meter walk test, functional reach test, activity specific balance confidence scale] and participation [Parkinson Disease Questionnaire-39] were assessed at baseline, 6, 12, 18 and 24 months.
RESULTS: Using generalized estimating equations at least one exercise behavior was a significant predictor across most of the models ($p \leq 0.026$), with higher RPE predicting better outcomes in all activity and participation domains. Younger age, male gender and lower disease severity also significantly predicted better outcomes over time ($p \leq 0.041$).
CONCLUSIONS: Exercise behaviors contributed to activity and participation-based outcomes over two years in exercisers with PD. Participation in high-intensity exercise programs may enhance maintenance of health and function over time in individuals with PD.

Keywords: Parkinson disease, exercise, intensity, boxing, participation

1. Introduction

Parkinson disease (PD) is a progressive neurodegenerative disorder that affects over one-half million people in the United States (Kowal, Dall, Chakrabarti, Storm, & Jain, 2013). PD is characterized by deterioration of motor and non-motor symptoms that span the spectrum of disability as defined by the International Classification of Functioning, Disability and Health (ICF) (Raggi et al., 2011). The natural progression of motor impairments and activity limitations in people with PD ranges from 2–7% annually (Alves, Wentzel-Larsen, Aarsland, & Larsen, 2005; Schrag et al., 2007). However, clinical progression of PD is highly variable among individuals with the disease, complicated by heterogeneity of symptoms (Post, Merkus, de Haan, & Speelman, 2007). While demographic and disease characteristics such as age, longer disease duration, and cognitive dysfunction predict a more rapid decline in PD (Alves et al., 2005; Velseboer et al., 2013), few studies have taken into consideration personal factors such as the exercise

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behaviors of their sample within prediction models (Oguh, Eisenstein, Kwasny, & Simuni, 2014; Rafferty et al., 2017).

Accumulating evidence within both animal and human research paradigms suggests the potential for exercise-induced modification of disease progression in persons with PD (Fisher et al., 2013; Fisher et al., 2008; Toy et al., 2014; Vučkovič et al., 2010). Authors of a large retrospective cohort study of people with PD reported that regular exercise (>150 min/week) is associated with better physical function, mobility, and quality of life, along with less disease progression than those with PD who exercise a smaller amount or not at all (Oguh et al., 2014). While this study provided important evidence for the value of amount of exercise, little is known of the benefits of other exercise behaviors such as intensity (exertion/work) or mode. Therefore, the purpose of this longitudinal, cohort study was to determine factors that predict outcomes across domains of the ICF over two years in exercisers with PD. We hypothesized that exercise behaviors such as, minutes per week, intensity and mode would significantly contribute to the outcomes.

2. Methods

2.1. Participants

Convenience sampling was used to recruit volunteers from local PD exercise programs and from clinics that treat people with PD. Flyers were distributed at PD support groups and PD symposiums throughout Central Indiana. One hundred and two individuals with PD were examined for eligibility. Eighty-eight of those individuals met the study criteria and were enrolled in this two-year longitudinal cohort study. Inclusion criteria for enrollment were: 1) diagnosis of idiopathic PD; 2) living within the community; 3) stage 1 through 4 on the Hoehn and Yahr scale (Goetz et al., 2004); 4) at least 21 years of age; 5) able to follow at least three-step verbal commands; 6) able to travel to and from all research measurement sessions. Exclusion criteria at enrollment included 1) pre-existing neurological condition other than PD, and 2) previous brain surgery (e.g. deep brain stimulator). All participants signed an informed consent document approved by the University of Indianapolis Institutional Review Board before beginning each testing session.

2.2. Procedures

Participants completed a total of five testing sessions, once every six months over a period of two years (baseline, 6, 12, 18, 24 months). Participants were instructed to take their anti-Parkinson medications one hour prior to each testing session to ensure they were tested during the "on" state of their medication. Time of day (am or pm) tested was held consistent across testing sessions as participant schedules permitted. Testing sessions were completed at a local fitness facility or a university lab setting with the site held constant for each participant for the duration of the study. Evaluators consisted of 12 entry-level Doctor of Physical Therapy students who were trained to follow a standardized testing protocol by the principal investigator. Student researchers were supervised by the principal investigator (SCM) throughout data collection to ensure testing procedures were followed. Order of outcome measures was randomized to reduce test order bias.

Age, sex, PD characteristics (time since diagnosis, Hoehn and Yahr scale), and co-morbidities were collected at the baseline testing session as these were identified in previous study findings (Alves et al., 2005; Velseboer et al., 2013; Zhao et al., 2010) as having an impact on outcomes of individuals diagnosed with PD. Co-morbidities were classified using the reliable Charlson Comorbidity Index (CCI) (Bernardini, Callen, Fried, & Piraino, 2004; Charlson, Pompei, Ales, & MacKenzie, 1987). The CCI contains 16 categories of co-morbidities which are given assigned weights of 1, 2, 3 or 6. From this weighted score the adjusted risk of one-year mortality is determined. The overall comorbidity score reflects the cumulative increased likelihood of one-year mortality; the higher the score, the more severe the burden of comorbidity. The CCI scores are classified as 1-2 mild, 3-4 moderate risk, with ≥ 5 considered severe risk of mortality (Huang et al., 2014).

Exercise behaviors [minutes of exercise per week, peak rate of perceived exertion (RPE) during exercise, and mode] were collected at each testing session. Peak RPE was reported as the participant's highest perceived level of exertion typically achieved during exercise using Borg's Rating of Perceived Exertion (6–20) Scale (Borg, 1998). Rate of perceived exertion is a reliable method of determining exercise intensity in persons with PD (Hooker et al., 1996). Weekly exercise logs were used to assist participants in tracking minutes of exercise per week and peak RPE during exercise. At each testing session, data from

the logs were used to confirm mean minutes of exercise and peak RPE reported by participants for that six month time period. Mean minutes of exercise per week and mean RPE were calculated across the two years of the study for analysis. Mode of exercise was based on each participant's self-selected exercise that they most often participated in within the six months prior to each testing session. Mode of exercise was recorded as either traditional exercise (e.g. running, walking, biking, home videos, PD-specific general exercise class or water aerobics) or non-traditional boxing exercise if the participant's primary mode of exercise was boxing or a boxing-based exercise class. For analysis, mode of exercise was determined as the primary mode of exercise reported in at least three testing sessions.

Outcome measures across ICF domains of body function impairment [grip strength], activity [comfortable 10-meter walk test (10MWT), functional reach test (FRT), activities-specific balance confidence scale (ABC)] and participation [Parkinson Disease Questionnaire-39 (PDQ-39)] were assessed at each testing session. Given the various exercise parameters expected from our sample we chose outcome measures that included upper and/or lower body movements across the ICF domains.

Grip strength is a reliable and valid measure of body function related to upper limb strength (Schaubert & Bohannon, 2005). A standardized testing procedure (Schaubert & Bohannon, 2005) was conducted using the Jamar handheld dynamometer (Lafayette Instrument Company, Lafayette, IN, USA). Participants performed three trials of maximal isometric effort for 3–5 seconds each for the dominant and non-dominant hands. The mean force in pounds for each hand was calculated and normalized to the participant's body weight.

The comfortable 10MWT is an activity-based measure this is a reliable and valid assessment of overground walking speed in people with PD (Combs, Diehl, Filip, & Long, 2014; Steffen & Seney, 2008). Three trials of the 10MWT were administered in an open hallway along a 14 meter walkway. Participants were timed for the middle ten meters and the mean time was converted to meters/second. Participants were instructed to walk at a self-selected pace using their typical way of walking (Combs et al., 2014; Flansbjer, Holmbäck, Downham, Patten, & Lexell, 2005).

The FRT was used to assess balance and is a reliable and valid measure of margins of standing stability in persons with PD (Steffen & Seney, 2008). Participants were instructed to raise their dominant arm parallel to the floor with their elbow fully extended and then reach forward as far as possible without losing their balance, lifting their feet or touching any other surface (Duncan, Weiner, Chandler, & Studenski, 1990). The mean of three trials was calculated and recorded in centimeters.

The ABC is a self-report measure of balance self-efficacy and confidence in performing activities in various environments (Dal Bello-Haas, Klassen, Sheppard, & Metcalfe, 2011; Steffen & Seney, 2008). It is valid and reliable for patients with PD (Dal Bello-Haas et al., 2011; Steffen & Seney, 2008). Participants rated their confidence from between 0% (no confidence) and 100% (complete confidence). The mean of the sixteen items was calculated and reported as a percent of balance confidence.

The PDQ-39 is a participation-based measure of quality of life for people with PD (Hagell & Nygren, 2007). For the purpose of this study, we chose to report the summary index as it relates to function and well-being across the spectrum of eight health-related domains (Jenkinson, Fitzpatrick, Peto, Greenhall, & Hyman, 1997). Items are rated on a 5-point Likert scale and totaled on a 0–100% scale with lower scores indicating better perception of health-related quality of life.

2.3. Data analysis

Participants who completed at least three of the five testing sessions across the two-year time period were included in the current analysis ($n = 74$). Excluded from the analysis were five participants (5.7%) who did not return after baseline and nine participants (10.2%) who did not return after the 6-month follow-up test, all completing only one or two testing sessions. Reasons for dropping out included: unable to contact, moved from area, scheduling conflict, transportation difficulty and other health related complications. Of the participants included in the final analysis, ten (11.4%) had one testing session missing and six (6.8%) had two testing sessions missing.

Data were analyzed using IBM SPSS 23.0 (IBM Corp., Armonk, NY) and all tests were two-tailed with statistical significance set at $p < 0.05$. Normality of the data was determined using the Shapiro-Wilk test. Descriptive statistics were conducted to describe the baseline characteristics of the total sample, as well as the analyzed and excluded participants. Categorical data are presented as frequencies and percentages, while continuous data are reported as means and

standard deviations or medians and interquartile ranges, dependent on whether or not the data were normally distributed. Generalized estimating equations (GEE) methodology was used to account for repeated measurements and the impact of variables on trends in the ICF domain scores over time. Separate analyses were performed for each of the outcome measures.

General estimating equations are well-suited for analyzing data with repeated measures and can handle missing data (Ma, Mazumdar, & Memtsoudis, 2012). Generalized estimating equations account for correlation of repeated measures from the same participant by computing a working correlation matrix and produces marginal population-average effect estimates (Shults, Sun, & Tu, 2009). Several working correlations were considered and the quasi-likelihood under the independence model criterion statistic was used to select the final working correlation structure. For all models, the autoregressive correlation structure was most suitable. All GEE models were fit with normal distribution, the identify link function, and autoregressive correlation structure using the SPSS GENLIN procedure. By using REPEATED statement, the correlations within repeated measures were taken into account. Linear time variable (visit) was centered at baseline to allow for interpretation of change over time. Covariates considered in the model as potential predictors included baseline demographics and PD characteristics, minutes of exercise/week and mean peak RPE. Prior to conducting the GEE modeling, the relationship between covariates was explored. Only covariates that were significant at $p < 0.05$ were retained in the final model. In assessing whether the assumption of multicollinearity was met, it was found that there was a significant relationship between the RPE and mode of exercise. Exercise mode was a significant predictor of RPE ($p < 0.001$). Models were conducted using either mode of exercise or RPE. Those using RPE resulted in the best quasi-likelihood than models with exercise mode; therefore, mode of exercise was not used as a covariate. The Wald chi-square test was used to determine if the covariate was a significant predictor of the outcome.

3. Results

Descriptive statistics for the total sample, as well as analyzed and excluded cohorts are reported in Table 1. The majority of participants were male with a mean age of 66.4 (9.3) years. The sample of participants ranged from stages 1–4 on the Hoehn and Yahr scale (stages 3 and 4 were combined for analysis due to the small number of participants in Hoehn and Yahr stage 4) and was a median 65 months from PD diagnosis. An average of over 224 minutes per week was spent exercising by the sample at an average peak RPE of 13.6 (2.1). The analyzed cohort was significantly a greater median number of months since PD diagnosis ($p = 0.02$) and had higher median non-dominant grip strength compared to the excluded cohort ($p = 0.02$).

The generalized estimating equation models are reported in Table 2. With exception of the PDQ-39 Summary Index, the Hoehn and Yahr Scale stage 3/4 and age were significant predictors of each ICF domain ($p \leq 0.037$). Less disease severity and younger age predicted higher scores across time. Sex was also a significant predictor in several of the models ($p \leq 0.041$), as males predicted better scores related to dominant and non-dominant grip strength and the 10MWT over time. At least one of the exercise behaviors, minutes of exercise per week and/or peak RPE, was a significant predictor in all of the models ($p \leq 0.026$) except grip strength. Higher peak RPE was a significant predictor of improved outcomes in all of the activity and participation domains. Time (visit) was only a significant predictor for the ABC ($p \leq 0.041$).

4. Discussion

Consistent with evidence in healthy adults (Bohannon, 1997; Samson et al., 2001; Steffen, Hacker, & Mollinger, 2002; Yorke, Curtis, Shoemaker, & Vangsnes, 2015), the findings of the current study show that younger age and male sex were significant contributors to most impairment and activity based outcome models predicting maintenance of higher scores across time. With the exception of the PDQ-39, Hoehn and Yahr stage significantly contributed to all models. As one would expect, being classified as stage 3 significantly predicted greater impairment in relation to stage 1. For FRT, stage 2 was also a significantly predictor in relation to stage 1. These results indicate that moderate PD severity predicted greater impairment and activity limitations.

Exercise behaviors also played a significant role across all outcome measures in the current study except grip strength. The most common exercise behavior to remain in the final models was peak exercise intensity as measured by the RPE scale.

Table 1
Demographics, PD characteristics, and outcomes for total sample, analyzed and excluded participants

	Total Sample $n = 88$ Mean (SD)	Included Participants $n = 74$ Mean (SD)	Excluded Participants $n = 14$ Mean (SD)
Age (years)	66.44 (9.33)	66.72 (8.40)	65.00 (13.58)
Male sex n (%)	61 (69)	54 (73)	7 (50)
Months since diagnosis*	65.00 (62.00)	69.00 (76.00)	32.00 (45.00)†
Hoehn & Yahr Scale n (%)			
Stage 1	41 (46.6)	38 (51.4)	3 (21.4)
Stage 2	22 (25.0)	17 (23.0)	5 (35.7)
Stage 3/4	25 (28.4)	19 (25.7)	6 (42.9)
Comorbidity Index*	2.00 (1.00)	2.00 (1.00)	3.00 (3.00)
Minutes of exercise/week	224.39 (123.93)	224.25 (116.24)	225.56 (184.74)
Peak RPE	13.60 (2.06)	13.62 (1.92)	13.44 (3.20)
Grips strength dominant (lbs.)	0.45 (0.13)	0.46 (0.13)	0.39 (0.13)
Grip strength non-dominant (lbs.)*	0.42 (0.15)	0.43 (0.12)	0.35 (0.14)†
10MWT (m/s)	1.21 (0.25)	1.23 (0.23)	1.12 (0.30)
FRT (cm)	25.10 (6.82)	25.49 (6.42)	23.04 (8.66)
ABC*	88.75 (24.06)	88.75 (23.28)	83.13 (31.02)
PDQ-39 Summary Index (%)*	16.59 (15.37)	15.36 (14.08)	25.52 (19.27)

*median (interquartile range) reported; † significant difference between included and excluded cohorts at $p < 0.05$; RPE = Rate of Perceived Exertion; 10MWT = comfortable 10-meter walk test; FRT = functional reach test; ABC = Activities Specific Balance Confidence Scale; PDQ-39 = Parkinson disease questionnaire-39.

Based on these results, every one point increase in peak RPE significantly predicted an increase of 0.03 meters/second in walking speed, 0.80 centimeters in forward reaching, and 1.75 percentage points in balance confidence on the ABC scale. In addition, a one point increase in peak RPE predicted a 1.55 point decrease (i.e. improvement) in self-perceived health-related quality of life on the PDQ-39 summary index. Despite amount of exercise (minutes per week) being previously identified as a vital factor for improved function and reducing progression of PD symptoms (Oguh et al., 2014; Rafferty et al., 2017), in the current study it only remained as a significant factor related to margin of stability with forward reaching on the FRT. In that case, each additional minute of exercise indicated decreased forward reach by 0.01 centimeters. While it is unknown if this change is meaningful, our results indicate the need to further investigate all types of exercise behaviors, in order to better understand their contributions to sustained health and function in persons with PD.

Self-reported peak RPE was a significant factor in most models suggesting that higher levels of exercise intensity may be important to maintaining better function and quality of life over time for persons with PD. In the current study, mode of exercise was not included as a potential predictor in any models, as it was significantly related to peak RPE. While mode of exercise varied among participants, 41 out of 74 participants in the analyzed cohort reported regularly participating in non-traditional boxing training over the two years of the study. The boxing program in which all boxers in this study attended (Rock Steady Boxing, Indianapolis, IN) incorporates higher-intensity interval training with boxers encouraged to exercise as intensely as tolerated for 2–4 minute bouts as they perform various boxing activities (hitting speed bags, heavy bags, etc.) and/or different agility drills (jumping rope, fast-paced footwork, etc.) followed by short, 1-2 minute rest periods. This potentially explains why those who attended boxing had a significantly higher self-perceived level of peak RPE compared to all others who partook in more traditional modes of exercise. High-intensity exercise programs have shown promise in promoting short-term functional and neurophysiologic improvements in people with PD (Combs et al., 2011; Dibble et al., 2006; Fisher et al., 2008; Rose, Løkkegaard, Sonne-Holm, & Jensen, 2013). More specifically, high-intensity interval training is a favorable mode of exercise for improving cardiorespiratory fitness in healthy populations (Milanovič, Sporiš, & Weston, 2015). However, it has not yet been found to be superior to continuous training protocols for people with PD (Pohl, Rockstroh, Rückriem, Mrass, & Mehrholz, 2003; Uc et al., 2014). Nonetheless, in the current sample it is impossible to discern whether non-traditional boxing mode or higher peak RPE contributed more so to the improved activity and walking function overtime. Thus, future research should take into consideration how both mode of exercise and intensity contribute to outcomes in

Table 2
Generalized estimating equation models

Variable	*p*	Exp (B)	95% CI
Grip Strength, dominant			
Sex (female)	<0.001	–0.90	–0.14, –0.04
Hoehn & Yahr Scale			
Stage 2	0.464	0.02	–0.04, 0.09
Stage 3/4	0.025	–0.06	–0.12, –0.01
Age (years)	<0.001	–0.01	–0.01, –0.00
Grip Strength, non-dominant			
Sex (female)	<0.001	–0.08	–0.13, –0.04
Hoehn & Yahr Scale			
Stage 2	0.547	0.02	–0.04, 0.07
Stage 3/4	0.010	–0.06	–0.11, –0.02
Age (years)	<0.001	–0.01	–0.01, –0.00
10MWT			
Sex (female)	0.041	–0.10	–0.19, –0.00
Hoehn & Yahr Scale			
Stage 2	0.472	0.04	–0.07, 0.16
Stage 3/4	0.003	–0.16	–0.26, –0.05
Age (years)	0.004	–0.01	–0.01, –0.00
Peak RPE	0.001	0.03	0.01, 0.05
FRT			
Hoehn & Yahr Scale			
Stage 2	0.003	–3.44	–5.71, –1.17
Stage 3/4	<0.001	–5.58	–8.71, –2.44
Age (years)	0.020	–0.16	–0.29, –0.03
Exercise Minutes	0.008	–0.01	–0.02, –0.00
Peak RPE	0.004	0.80	0.25, 1.34
ABC			
Hoehn & Yahr Scale			
Stage 2	0.816	–0.89	–8.37 – 6.60
Stage 3/4	0.037	–9.47	–18.38, –0.57
Age (years)	0.027	–0.53	–0.99, –0.06
Peak RPE	0.026	1.75	0.21, 3.29
Visit	0.041	–0.90	–1.75, –0.04
PDQ-39 Summary Index			
Peak RPE	0.011	–1.55	–2.74, –0.35

RPE = Rate of Perceived Exertion; 10MWT = comfortable 10-meter walk test; FRT = functional reach test; ABC = Activities Specific Balance Confidence Scale; PDQ-39 = Parkinson disease questionnaire-39.

persons with PD, specifically over a longer period of time.

Individuals with PD with higher self-efficacy are more likely to engage in physical activity (Ellis et al., 2011). On the other hand, higher intensity exercise has been reported to increase self-efficacy after training in other populations (Olsen, Telenius, Engedal, & Bergland, 2015; Singh et al., 2012). In reality, this may mimic the 'did the chicken or the egg come first' situation. Higher self-reported peak RPE during exercise predicted higher scores overtime in balance self-efficacy on the ABC in the current study. Each one point increase on the RPE scale indicated an almost 2 point increase on the ABC. While we cannot determine the mechanism for this finding in our cohort of exercisers with PD, we speculate that either those with higher balance self-efficacy are more likely to participate in more intense exercise programs, such as boxing, or that overtime, participation in more intense exercise fosters a higher perception of balance self-efficacy.

Perhaps most promising from the current results is that change over time (visit), indicating a progression of disease symptoms, did not significantly remain in the models for any of the outcome measures except the ABC. The ABC scores decreased over time, suggesting a decline in self-perceived balance confidence. However, the sample of exercisers with PD maintained consistent levels of ability across all evaluator assessed performance-based outcomes for two years. With previous studies indicating an annual decline in function in general samples with PD (Alves et al., 2005; Schrag et al., 2007), our findings add to the evidence signifying the importance in considering personal factors, such as exercise behaviors, in the long-term progression of PD. Future studies should take into consideration various exercise behaviors, particularly intensity of training when examining longitudinal outcomes.

4.1. Study limitations

This study is limited in that it was underpowered to consider other factors that could have an impact on progression of PD, including cognition and changes in medications. Thus, their effects on the models are unknown. Also, pre-study exercise habits of the participants were not recorded and could have influenced the long-term outcomes. Categorization into mode of exercise was based on each participant's self-reported exercise regimen they most often participated in for the six months prior to each testing session. We did not take into account other exercise programs they may have participated in during that time.

5. Conclusion

Along with common factors of age, sex and Hoehn and Yahr scale, exercise behaviors were significant contributors to the outcome measures over two years in this sample of exercisers with PD. Peak training intensity during exercise significantly contributed to most models, indicating that greater intensity of exercise may promote better function across domains of the ICF.

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Conflict of interest

The authors report no conflicts of interest.

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