5-17-2019

The Moderation Effect of BDNF Genotype and Self-Reported Lifetime Physical Activity Habits on Postural Instability in Parkinson's Disease

Samantha Johnson
University of Nevada, Las Vegas

Tyler Ormsby
University of Nevada, Las Vegas

THE MODERATION EFFECT OF BDNF GENOTYPE AND SELF-REPORTED LIFETIME PHYSICAL ACTIVITY HABITS ON POSTURAL INSTABILITY IN PARKINSON'S DISEASE

By

Samantha Johnson

Tyler Ormsby

A doctoral project submitted in partial fulfillment

of the requirements for the

Doctor of Physical Therapy

Department of Physical Therapy

School of Allied Health Sciences

Division of Health Sciences

The Graduate College

University of Nevada, Las Vegas

May 2019

UNLV | GRADUATE COLLEGE

Doctoral Project Approval

The Graduate College
The University of Nevada, Las Vegas

May 17, 2019

This doctoral project prepared by

Samantha Johnson

Tyler Ormsby

entitled

The Moderation Effect of BDNF Genotype and Self-Reported Lifetime Physical Activity Habits on Postural Instability in Parkinson's Disease

is approved in partial fulfillment of the requirements for the degree of

Doctor of Physical Therapy
Department of Physical Therapy

Daniel Young, Ph.D.
Research Project Coordinator

Kathryn Hausbeck Korgan, Ph.D.
Graduate College Dean

Kai-Yu Ho,, Ph.D.
Research Project Advisor

Merrill Landers, Ph.D.
Chair, Department of Physical Therapy

ABSTRACT

Background and Purpose: Brain-derived neurotrophic factor (BDNF) levels play an important role in neuroplasticity in normal and neurologically compromised individuals. Studies suggest that BDNF levels increase in response to physical activity and are also affected by genotype. In individuals with Parkinson's Disease (PD), it is not known if physical activity habits and BDNF genotype modulate this neuroprotective response. The purpose of this study was to determine if BDNF genotype interacts with lifetime self-reported physical activity levels to affect age of disease onset and severity of PD symptoms, specifically gait, balance, and motor dysfunction.

Methods: Included in this study were 76 individuals with idiopathic PD. DNA collected from buccal cells was used to determine BDNF genotype. Self-reported measures included a modified version of the Lifetime Physical Activity Questionnaire (LPAQ), the Fear of Falling Avoidance Behavior Questionnaire (FFABQ), the Activities-Specific Balance Confidence scale (ABC), and demographic information. Tester-administered measures included the Mini-Balance Evaluations Test (MiniBESTest) – a gait and balance performance battery, and the Movement Disorder Society – Unified Parkinson's Disease Rating Scale III (MDS-UPDRS-III) – an observation assessment of motor function.

Results: There was no significant interaction between BDNF genotype and self-reported levels of physical activity on measures of postural instability. However, participants who, on average, reported engaging in more moderate and vigorous activities during their 20s-40s were found to benefit from a potential neuroprotective effect of such activity. Higher reported moderate activity during this time frame was associated with later disease onset, and a greater number of average hours per week of vigorous activity was associated with better gait and balance scores.

Discussion: Fortunate genetics and a patient reported history of high, habitual physical activity throughout the lifespan may be associated with improved function in individuals with PD. Further research is needed to confirm this finding as our analyses were underpowered due to small sample size.

Still, our findings confirm the importance of living an active lifestyle, particularly, engaging in more moderate and vigorous activities during 20s-40s. This information may improve the clinicians' ability to develop individualized treatment plans, can guide individuals at risk for developing PD, and reinforces the benefits of healthy lifestyle modifications.

ACKNOWLEDGEMENTS

This research study was made possible by the UNLV PT Department Student Opportunity Grant. The authors would like to thank Dr. Merrill Landers, PT, DPT, PhD for his mentorship as principle investigator of this study. Research and data collection were also completed with the assistance of Kyle Johnson, DPT, Danielle Salgo, DPT, Jessica Zorn, DPT, and Kathleen Nagle from the physical therapy research department at UNLV. The authors would also like to thank Dr. Szu-Ping Lee, Dr. Kai-Yu Ho, Dr. Daniel Young, and Dr. Jing Nong Liang for their additional help with this project.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

INTRODUCTION

Epidemiologic research provides evidence that moderate to vigorous aerobic exercise performed throughout one's lifespan decreases the risk of developing PD.[1-4] However, the mechanism for this protection is not fully understood. One hypothesis is that these effects are mediated in part by increased production of brain-derived neurotrophic factor (BDNF).[5] BDNF is a neurotrophin, produced in both the brain and peripheral tissue, and is critical in neurogenesis and neuroplasticity.[6]

Increased levels of circulating BDNF promote cell division, regulate neuronal plasticity, and exert a protective effect on dopaminergic neurons.[7-11] A single bout of high-intensity aerobic exercise increases circulating BDNF[10 12 13] and is associated with increased motor learning and declarative memory in healthy subjects[13] and those with PD.[12] The brain has been shown to be a source of circulating BDNF at rest, and may be a significant contributor to increased plasma BDNF during and following aerobic exercise.[14] However, an injection of free BDNF into circulation does not result in increased BDNF concentration in the brain, due to its inability to cross the blood-brain barrier.[15 16]

Levels of BDNF production are mediated by a specific gene. A single nucleotide polymorphism (SNP) of this gene exists in which the valine at position 66 of the BDNF precursor polypeptide is substituted for methionine (known commonly as the Val66Met polymorphism).[17] The presence of this substitution ultimately decreases the amount of BDNF that is produced.[5] In mice, the homozygous Val/Val genotype results in the greatest production of BDNF after cerebral ischemic infarct.[18] Whereas, at certain stages of recovery the homozygous Met/Met genotype results in the lowest average production of BDNF, less than half of their Val/Val counterparts.[18] A correlation between mice and humans can be made based on the studies' design using mutated mice resembling human expression of the specific BDNF polymorphism.[18]

Initial studies suggest that this genetic polymorphism and aerobic activity levels may interact and moderate BDNF production simultaneously. For instance, participants who were post-stroke with a Val/Val genotype had a better response to aerobic exercises and activities to promote motor learning than participants with either the heterozygous or homozygous Met/Met genotypes.[19] While it appears unlikely that the Val66Met polymorphism alone affects the age of onset or severity of PD progression,[9] it is possible that an interaction between BDNF genotype and history of physical activity would. However, no studies have yet investigated the effect of and interaction between genotype and exercise on PD onset and severity or on physical function in this population.

The primary aim of our study was to determine if BDNF genotype and lifetime physical activity levels interacted to influence age of PD diagnosis and current disease severity. We predicted that individuals with a homozygous Val66Val genotype and those with higher lifetime physical activity levels would have a later disease onset and less severe current PD motor symptoms after controlling for years since onset. Another aim was to determine if the BDNF genotype and lifetime physical activity levels were predictive of current gait and balance measures while controlling for years since onset. We predicted that individuals with a homozygous Val66Val genotype and those with higher lifetime physical activity levels would have better performance on measures of gait and balance.

METHODS

Study Design

The study used a cross-sectional design wherein BDNF genotype and self-reported physical activity habits across the lifespan were evaluated for association with year of onset (self-report of age at diagnosis), PD motor symptoms, and measures of gait and balance function. BDNF Val66Met genotype

was determined by collecting buccal cells and polymerase chain reaction. This method is preferred as it is non-invasive, convenient and relatively inexpensive.

Physical activity levels were determined using a modified version of the Lifetime Physical Activity Questionnaire (LPAQ).[20] The questionnaire includes questions about time spent sitting, walking, performing moderate activity and performing vigorous activity during a total of seven life stages (teens, twenties, thirties, forties, fifties, during the five years before diagnosis with PD and during the time since diagnosis with PD). Self-reporting of habitual physical activity of various intensities across different stages of the lifespan has been shown to have reliability, validity and reproducibility in the LPAQ as well as by other developers of similar questionnaires.[21 22] Additionally, we tested reliability from a subset of participants in this study (n=15, age= 64.3±4.9 years; males= 10, females= 5; Montreal Cognitive Assessment (MoCA)=27.2, SD=2.0; years since diagnosis=8.1±5.5) by having participants complete the LPAQ twice separated by one week. An Intraclass Correlation Coefficient (ICC(3,1)) showed moderate and vigorous physical activity recollection ranged from .77 to .91 at all of the time points between 20-29 years to 5 years before diagnosis.[23] Walking and sitting were more variable for the same time periods (ICCs between .29-.82) and were subsequently not used in the analyses. The teen years were also low for all activity levels (ICCs<.55) and were, subsequently, not used in the analyses. Likewise, activity levels for the time since diagnosis were low (ICCs<.25) except for vigorous activity which was .91. Thus, the LPAQ reliability was good for moderate and vigorous physical activity at almost all time points.

PD motor symptoms were measured using the motor subscale (section 3) of the Movement Disorder Society – Unified Parkinson's Disease Rating Scale (MDS-UPDRS)[24] and the Hoehn & Yahr Scale.[25] The Hoehn & Yahr Scale shows stronger reliability and validity in categorizing the progression of PD than the Modified Hoehn & Yahr and was therefore selected for this study.[26] The MDS-UPDRS is the most widely

used scale for rating the severity of PD and the validity, inter-rater and intra-rater reliability of this instrument are well established.[27-29]

Gait and balance function were quantified using both subject-reported measures, including the Fear of Falling Avoidance-Behavior Questionnaire (FFABQ)[30] and the Activities-Specific Balance Confidence Scale (ABC),[31] as well as a clinician-administered measure, the Mini-BESTest,[32] all of which have good evidence for inter-rater and intra-rater reliability and construct validity in the PD population.

Sample Size Calculation

Sample size was estimated using the multiple regression module from PASS 16.0 (NCSS, LLC. Kaysville, Utah, USA, ncss.com/software/pass) for the two regressions proposed for Aim 1. For the prediction of disease onset, 37 participants were needed (α=0.05, 80% power) with one variable (BDNF genotype) conservatively estimated to have a low R^2 of 0.150 entered first and two other variables (average moderate 20s to 40s physical activity; average 20s to 40s vigorous physical activity) entered next at low to moderate R^2 of 0.200. For the prediction of current PD motor symptom severity (UPDRS III), 45 participants were needed (α=0.05, 80% power) with two variables entered first (BDNF genotype, years since diagnosis) and conservatively estimated (R^2 of 0.150) and four other variables (average moderate 20s to 40s physical activity; average 20s to 40s vigorous physical activity; moderate activity since diagnosis; vigorous physical activity since diagnosis) at low to moderate R^2 of 0.200.

Participants

Seventy-six individuals with PD participated. To be included, participants had to have idiopathic PD diagnosed by a neurologist, based on the Movement Disorder Society (MDS) Clinical Diagnostic Criteria.[18] Participants with a MoCA score below 20.5 were excluded from the analysis.[33] The MoCA has

excellent test-retest reliability with an ICC = 0.97 and good validity for the detection of mild cognitive impairment in people with PD. [26 34] Demographic data collected from each participant included gender, age, year of diagnosis, fall history, disease stage on the Hoehn and Yahr scale, medications, and time since last medication dosage. Recruitment included snowball strategies with participants and recruiting visits to PD support groups, community gyms, senior centers, and movement disorder neurologist referrals. All participants were consented per the protocol approved by the University of Nevada, Las Vegas Institutional Review Board. Because of the design of this study, two different sample sizes were used for the analyses. For the primary aim of disease onset, participants diagnosed with early onset PD (<50 years at diagnosis) were eliminated from the analysis because their physical activity levels would represent averages from 20s to 40s only. This resulted in 60 participants for that analysis (Figure 1). For all other analyses, 54 participants were analyzed (Figure 2). Because deep brain stimulation (DBS) would be potentially confounding for PD motor symptoms, participants who had had the procedure were excluded from those analyses.

Figure 1. Flow diagram for prediction of age at onset subjects.

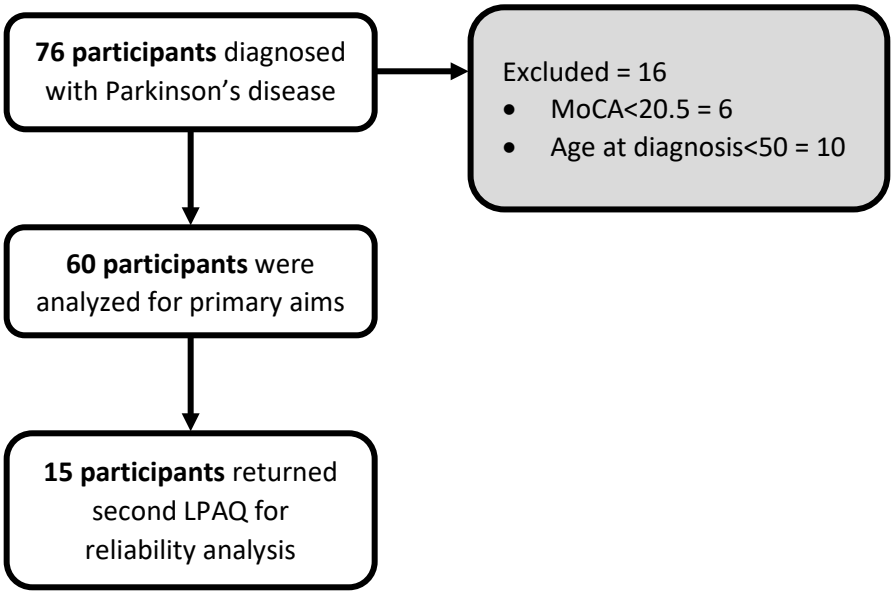
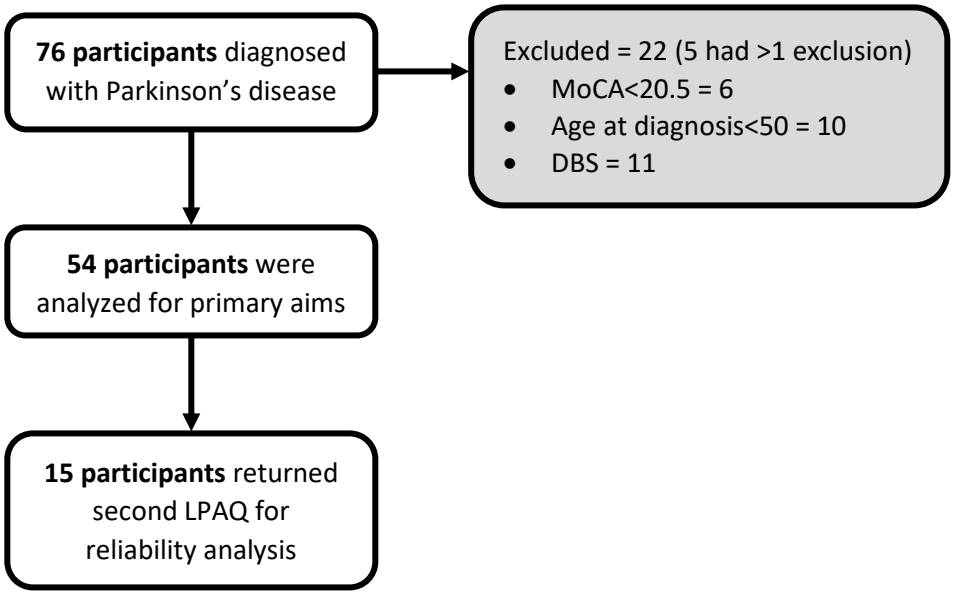


Figure 2. Flow diagram for prediction of PD motor symptoms and measures of gait and balance subjects.



Data Analysis

Data were analyzed using SPSS version 24.0 (SPSS Inc, Chicago, Illinois) at $\alpha = 0.05$. Hierarchical, multiple linear regression analyses were conducted to examine the relationship between predictor variables (BDNF genotype and lifetime physical activity levels) on the following dependent variables: disease onset (age at diagnosis), PD motor symptoms (MDS-UPDRS III), and measures related to gait and balance (MBT, ABC, mFFABQ). For disease onset (year of diagnosis), the following variables were entered into the hierarchical model: step 1 (BDNF genotype) and step 2 (average moderate 20s to 40s physical activity; average 20s to 40s vigorous physical activity). For PD motor symptoms (MDS-UPDRS III) and gait and balance (MBT, ABC, mFFABQ), the following were entered into the model: step 1 (BDNF genotype, years since diagnosis) and step 2 (average moderate 20s to 40s physical activity; average 20s to 40s vigorous physical activity; moderate activity since diagnosis; vigorous physical activity since diagnosis). Dependent variable outliers, defined as those with standardized residual values above 3.3 or below -3.3, were screened for removal from the analyses (none identified). Normality, collinearity diagnostics (Variance Inflation Factor cutoff of 10), and bivariate correlations were also conducted. There were no

major deviations from normality. Due to multicollinearity, the physical activity for the 20s, 30s, and 40s was averaged rather than entered into the regression analyses individually.

RESULTS

Age of PD diagnosis

The final hierarchical regression model for prediction of age of onset produced an R^2 = 0.146 (adjusted R^2 = 0.099), F(3,58)=3.125, p=.033 (Table 1); however, the only significant variable in the final model was the average reported amount of moderate physical activity performed during 20s to 40s (p=.009). Neither BDNF genotype (p=.377) or the average amount of vigorous activity during 20s to 40s (p=.664) were statistically significant (Table 2). When the average amount of vigorous activity performed during the ages 20s to 40s was removed from the model, the final model R^2 was 0.143 (adjusted R^2=0.112) and was still significant (p=.013). When BDNF genotype was removed from the model, the final R^2 decreased to 0.115 (adjusted R^2=0.100) but was still significant (p=.008).

Table 1. Model summary for predication of age at PD diagnosis.

Model	R	R Square	Adjusted R Square	Std. Error of the Estimate
1	.155	.024	.007	7.98
2	.382	.146	.099	7.60

Table 2. Coefficients for regression model on age at PD diagnosis.

Model		Unstandardized Coefficients		Standardized Coefficients	t	p value
		B	Std. Error	Beta		
1	(Constant)	66.450	3.123		21.277	.000
	BDNF genotype	-2.669	2.257	-.155	-1.183	.242
2	(Constant)	62.631	3.329		18.813	.000
	BDNF genotype	-1.928	2.166	-.112	-.890	.377
	Moderate physical activity 20s to 40s	.270	.100	.372	2.701	.009
	Vigorous physical activity 20s to 40s	-.052	.120	-.060	-.437	.664

PD motor symptoms

The hierarchical regression for UPDRS III was not statistically significant, F(6,52)=.867, p=.526. In the final model, none of the variables were statistically significant (ps ≥ .140).

Gait and balance

The final hierarchical regression for MBT was statistically significant, F(6,52)=2.304, p=.0499. In the final model, 23.1% of the variance was explained (R^2=.231; adjusted R^2=.131) (Table 3). Years since diagnosis (p=.014) and average vigorous physical from 20s to 40s (p=.047) were the only two statistically significant predictors in the final model (Table 3).

Table 3. Model summary for predication of MBT score.

Model	R	R Square	Adjusted R Square	Std. Error of the Estimate
1	.309	.096	.059	5.631
2	.481	.231	.131	5.413

Table 4. Coefficients for regression model on MBT score.

Model		Unstandardized Coefficients		Standardized Coefficients	t	p value
		B	Std. Error	Beta		
1	(Constant)	23.703	2.586		9.166	.000
	Genotype	.836	1.658	.068	.504	.616
	Years since diagnosis	-.394	.177	-.300	-2.228	.030
2	(Constant)	26.371	2.871		9.186	.000
	BDNF genotype	.574	1.686	.047	.340	.735
	Years since diagnosis	-.444	.173	-.338	-2.562	.014
	Moderate physical activity 20s to 40s	-.100	.076	-.190	-1.327	.191
	Vigorous physical activity 20s to 40s	-.219	.107	-.320	-2.037	.047
	Moderate physical activity since diagnosis	.112	.189	.098	.590	.558
	Vigorous physical activity since diagnosis	.062	.165	.063	.373	.711

For the ABC, the final hierarchical model explained 24.7% of the variance, F(6,52)=2.508, p=.035 (Table 5). In the final model, the only variable that was statistically significant was years since diagnosis (p=.002) (Table 6).

Table 5. Model summary for predication of ABC score.

Model	R	R Square	Adjusted R Square	Std. Error of the Estimate
1	.410	.168	.135	21.08
2	.497	.247	.148	20.91

Table 6. Coefficients for regression model on ABC score.

Model		Unstandardized Coefficients		Standardized Coefficients	t	p value
		B	Std. Error	Beta		
1	(Constant)	89.203	9.681		9.214	.000
	Genotype	.477	6.206	.010	.077	.939
	Years since diagnosis	-2.099	.662	-.409	-3.172	.003
2	(Constant)	100.011	11.090		9.018	.000
	BDNF genotype	-1.538	6.512	-.032	-.236	.814
	Years since diagnosis	-2.234	.669	-.436	-3.339	.002
	Moderate physical activity 20s to 40s	-.330	.292	-.160	-1.129	.265
	Vigorous physical activity 20s to 40s	-.496	.415	-.186	-1.197	.237
	Moderate physical activity since diagnosis	-.225	.731	-.051	-.308	.760
	Vigorous physical activity since diagnosis	.445	.637	.116	.698	.489

The final hierarchical model for the prediction of mFFABQ was not statistically significant, $F(6,52)=2.052$, $p=.078$. The final model explained 21.1% of the variance ($R^2=.211$; adjusted $R^2=.108$) and even though years since diagnosis was significant ($p=.007$), the overall model was not. All of the other variables were not statistically significant ($ps \geq .133$).

DISCUSSION

Our results suggest that self-reported moderate physical activity during the 3rd, 4th, and 5th decades of life is associated with age at diagnosis. Specifically, those who reported having spent more time participating in moderate physical activity during those three decades were older at diagnosis. This is consistent with the notion that exercise may be neuroprotective in PD and is consistent with several other studies that have shown that exercise/physical activity is associated with a lower risk of PD.[1-4 35-37]

Our results suggest that every hour increase in weekly moderate physical activity (unstandardized beta = .270) was associated with a PD diagnosis a little over a quarter of a year later. While this relationship is potentially important from a neuroprotective perspective, it should be noted that moderate physical activity only explained 10-14% of the variance of age of onset which suggests that a larger portion of the variance remains unexplained by our model; there are clearly other contributors. We had anticipated that BDNF might play a role in potentiating the neuroprotection but the low and non-significant correlations, though headed in the correct direction (i.e., val/val carriers having an older age at diagnosis), suggests that BDNF may only play a minor role.

Other studies have demonstrated similar neuroprotective effects of exercise in PD.[1 2 35 38] For example, Chen et al reported that men who performed greater baseline physical activity had a decrease risk of PD.[1] However, contrary to our findings, further analysis by Chen and colleagues revealed that only vigorous and not moderate activity was related to the lower risk of PD in their subjects.[1] It is important to note that their baseline measurements were recorded on subjects ages 30-55, which is an older and different lifespan period than our study. Sääksjärvi et al. reported that, compared to those who engaged in no heavy leisure-time activity, individuals who performed heavy physical activity were less likely to develop PD, relative risk = .27.[2] In their study, heavy leisure-time activity was defined as doing greater than 3 hours per week of activities such as jogging, skiing, or vigorous gardening.[2] A slight protective effect of physical activity was also described by Sasco et al, who found that belonging to a varsity team in college was associated with a lower nonsignificant risk of PD.[35] Moderate physical activity done during adulthood was also found to be linked to a reduced risk of PD.[35] Yang et al reported an inverse association between physical activity and PD as well. However, their team looked at total physical activity as compared to the other studies that focused on moderate and vigorous physical activity.[4] While the aforementioned studies are reporting a similar construct, there is one big difference. Those

studies were large retrospective cohort studies wherein a cohort of healthy individuals were tracked over time to see who would eventually develop PD. Thus, they were looking at how physical activity influenced the risk of PD. We used a cross-sectional design wherein only individuals already diagnosed with PD were included. While each of these studies in isolation is not strong for causal inference of neuroprotection in PD, the evidence for causal inference is enhanced by the number of studies supporting the construct, the consistency of results across different designs, the strength of associations, and the biological plausibility. Taken together, our results suggest a new way of investigating the potential protective effect of physical activity in PD.

While moderate lifetime physical activity was predictive of age at diagnosis, vigorous activity was not. On the surface, it seems logical that vigorous activity, much like moderate physical activity, would be associated with age at diagnosis. However, it is possible that vigorous activity, which is typically close or over the anaerobic threshold, would produce more inflammatory signals thereby increasing the inflammatory milieu of the individual.[39 40] Since inflammation is a known pathophysiologic mechanism and a potential disease trigger[41] it is possible that engaging in high amounts of vigorous exercise may tip the inflammatory balance to a potentially deleterious process. Thus, the issue of exercise/physical acitivty dosing warrants additional scientific exploration.

None of the predictor variables in our study were associated with current PD motor symptoms as measured by MDS-UPDRS-III score. We had anticipated that greater physical activity and a favorable BDNF genotype (i.e., more BDNF produced) would have produced a better neuroprotective environment[40 42 43] which presumably would have strengthened neural networks associated with motor function. This in turn was hypothesized to promote a slower and more protracted decline in motor function. However, our results did not support this notion.

Another noteworthy finding of this study is that two variables predicted gait and balance. First, higher balance performance (MBT scores) were achieved by those who engaged in higher amounts of vigorous physical activity during their 20s-40s. Evidence suggests that balance responds best to more intense, challenge-based training in older adults.[44 45] Our study suggests that more vigorous physical activity during 20s-40s may also have a carry-over effect on balance later in life. However, further research is needed to confirm this proposition. Second, we found that years since diagnosis was negatively correlated with balance. Essentially, the longer an individual had been diagnosed with PD the worse their gait and balance, represented by a lower MBT score. This is logical and consistent with the literature.[46 47]

Sample recruitment bias is also a major limitation. Most participants were recruited from other research studies, most of which investigated the effects of exercise, or were informed of the focus of the study prior to participating, leading to possible over reporting of physical activity. In fact, self-reported levels of physical activity were remarkably high for the sample tested at all age groups with 78% to 89% of the participants reporting having met Centers for Disease Control (CDC) recommendations for physical activity[48 49] at all stages of their lives. In comparison, only 51% of adults in the United States report meeting CDC guidelines for aerobic exercise.[50] Additionally, older adults tend to over-estimate the time they spend exercising.[51 52] A study by Tucker et al found that while 62% of a representative sample of Americans self-reported meeting 2008 Physical Activity Guidelines for Americans, only 9.6% of participants truly met the guidelines as measured by accelerometer, a pattern that was consistent at all age groups (20s, 30s, 40s, 50s, 60s, >70).[53] Thus, it is possible that participants in the present study also overestimated their physical activity levels and/or the sample may have been biased by volunteers who were more likely to be physically active. On the other hand, it is possible that participants at both ends of the physical activity spectrum exaggerated their activity levels relatively equally (non-differential

misclassification bias). In addition, it is possible that participants exaggerated their physical activity levels to avoid looking inactive to the research assistants, thinking that by reporting their actual levels they might be perceived as bearing partial responsibility for their PD. This type of participant bias is referred to as social desirability bias and it has been documented in the self-report of physical activity.[54] Lastly, it is important to bear in mind that physical activity also reflects work and it is possible that participants may have had occupations that required considerable physical activity.

CONCLUSION

Our results suggest that people with PD who reported more moderate physical activity from the 3rd through 5th decades of life were older at diagnosis when compared to those who reported lower levels of physical activity. Our results also indicate that more vigorous physical activity from the 3rd to the 5th decades of life was associated with better gait and balance function. As expected, lower MBT scores, indicating poor gait and balance performance, were seen in those who had been diagnosed with PD the longest. BDNF did not appear to play a large role in age at diagnosis or current PD motor symptoms.

REFERENCES

1. Chen H, Zhang SM, Schwarzschild MA, et al. Physical activity and the risk of Parkinson disease. *Neurology* 2005;64(4):664-9. doi: 10.1212/01.WNL.0000151960.28687.93
2. Saaksjarvi K, Knekt P, Mannisto S, et al. Reduced risk of Parkinson's disease associated with lower body mass index and heavy leisure-time physical activity. *Eur J Epidemiol* 2014;29(4):285-92. doi: 10.1007/s10654-014-9887-2
3. Tsai CH, Lo SK, See LC, et al. Environmental risk factors of young onset Parkinson's disease: a case-control study. *Clin Neurol Neurosurg* 2002;104(4):328-33.
4. Yang F, Trolle Lagerros Y, Bellocco R, et al. Physical activity and risk of Parkinson's disease in the Swedish National March Cohort. *Brain* 2015;138(Pt 2):269-75. doi: 10.1093/brain/awu323
5. Altmann V, Schumacher-Schuh AF, Rieck M, et al. Val66Met BDNF polymorphism is associated with Parkinson's disease cognitive impairment. *Neurosci Lett* 2016;615:88-91. doi: 10.1016/j.neulet.2016.01.030
6. Campos C, Rocha NB, Lattari E, et al. Exercise-induced neuroprotective effects on neurodegenerative diseases: the key role of trophic factors. *Expert Rev Neurother* 2016;16(6):723-34. doi: 10.1080/14737175.2016.1179582
7. Ferris LT, Williams JS, Shen CL. The effect of acute exercise on serum brain-derived neurotrophic factor levels and cognitive function. *Med Sci Sports Exerc* 2007;39(4):728-34. doi: 10.1249/mss.0b013e31802f04c7
8. Guerini FR, Beghi E, Riboldazzi G, et al. BDNF Val66Met polymorphism is associated with cognitive impairment in Italian patients with Parkinson's disease. *Eur J Neurol* 2009;16(11):1240-5. doi: 10.1111/j.1468-1331.2009.02706.x
9. Hong CJ, Liu HC, Liu TY, et al. Brain-derived neurotrophic factor (BDNF) Val66Met polymorphisms in Parkinson's disease and age of onset. *Neurosci Lett* 2003;353(1):75-7.
10. Mang CS, Campbell KL, Ross CJ, et al. Promoting neuroplasticity for motor rehabilitation after stroke: considering the effects of aerobic exercise and genetic variation on brain-derived neurotrophic factor. *Phys Ther* 2013;93(12):1707-16. doi: 10.2522/ptj.20130053
11. Nascimento CM, Pereira JR, Pires de Andrade L, et al. Physical exercise improves peripheral BDNF levels and cognitive functions in mild cognitive impairment elderly with different bdnf Val66Met genotypes. *J Alzheimers Dis* 2015;43(1):81-91. doi: 10.3233/JAD-140576
12. Bialecka M, Kurzawski M, Roszmann A, et al. BDNF G196A (Val66Met) polymorphism associated with cognitive impairment in Parkinson's disease. *Neurosci Lett* 2014;561:86-90. doi: 10.1016/j.neulet.2013.12.051
13. Smith AE, Goldsworthy MR, Garside T, et al. The influence of a single bout of aerobic exercise on short-interval intracortical excitability. *Exp Brain Res* 2014;232(6):1875-82. doi: 10.1007/s00221-014-3879-z
14. Rasmussen P, Brassard P, Adser H, et al. Evidence for a release of brain-derived neurotrophic factor from the brain during exercise. *Exp Physiol* 2009;94(10):1062-9. doi: 10.1113/expphysiol.2009.048512
15. Pilakka-Kanthikeel S, Atluri VS, Sagar V, et al. Targeted brain derived neurotropic factors (BDNF) delivery across the blood-brain barrier for neuro-protection using magnetic nano carriers: an in-vitro study. *PLoS One* 2013;8(4):e62241. doi: 10.1371/journal.pone.0062241
16. Zhang Y, Pardridge WM. Blood-brain barrier targeting of BDNF improves motor function in rats with middle cerebral artery occlusion. *Brain Res* 2006;1111(1):227-9. doi: 10.1016/j.brainres.2006.07.005

17. Cagni FC, Campelo C, Coimbra DG, et al. Association of BDNF Val66MET Polymorphism With Parkinson's Disease and Depression and Anxiety Symptoms. *J Neuropsychiatry Clin Neurosci* 2017;29(2):142-47. doi: 10.1176/appi.neuropsych.16040062
18. Qin L, Kim E, Ratan R, et al. Genetic variant of BDNF (Val66Met) polymorphism attenuates stroke-induced angiogenic responses by enhancing anti-angiogenic mediator CD36 expression. *J Neurosci* 2011;31(2):775-83. doi: 10.1523/JNEUROSCI.4547-10.2011
19. Di Lazzaro V, Pellegrino G, Di Pino G, et al. Val66Met BDNF gene polymorphism influences human motor cortex plasticity in acute stroke. *Brain Stimul* 2015;8(1):92-6. doi: 10.1016/j.brs.2014.08.006
20. Postuma RB, Berg D, Stern M, et al. MDS clinical diagnostic criteria for Parkinson's disease. *Mov Disord* 2015;30(12):1591-601. doi: 10.1002/mds.26424
21. De Vera MA, Ratzlaff C, Doerfling P, et al. Reliability and validity of an internet-based questionnaire measuring lifetime physical activity. *Am J Epidemiol* 2010;172(10):1190-8. doi: 10.1093/aje/kwq273
22. Friedenreich CM, Courneya KS, Bryant HE. The lifetime total physical activity questionnaire: development and reliability. *Med Sci Sports Exerc* 1998;30(2):266-74.
23. Johnson K, Salgo D, Zorn J, et al. The reliability of a self-report questionnaire about lifetime physical activity levels in people with Parkinson's disease. *Journal of Neurologic Physical Therapy* 2018;Posters:219.
24. Richards M, Marder K, Cote L, et al. Interrater reliability of the Unified Parkinson's Disease Rating Scale motor examination. *Mov Disord* 1994;9(1):89-91. doi: 10.1002/mds.870090114
25. Goetz CG, Poewe W, Rascol O, et al. Movement Disorder Society Task Force report on the Hoehn and Yahr staging scale: status and recommendations. *Mov Disord* 2004;19(9):1020-8. doi: 10.1002/mds.20213
26. Hoops S, Nazem S, Siderowf AD, et al. Validity of the MoCA and MMSE in the detection of MCI and dementia in Parkinson disease. *Neurology* 2009;73(21):1738-45. doi: 10.1212/WNL.0b013e3181c34b47
27. Nasreddine ZS, Phillips NA, Bedirian V, et al. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. *J Am Geriatr Soc* 2005;53(4):695-9. doi: 10.1111/j.1532-5415.2005.53221.x
28. Paillard T, Rolland Y, de Souto Barreto P. Protective Effects of Physical Exercise in Alzheimer's Disease and Parkinson's Disease: A Narrative Review. *J Clin Neurol* 2015;11(3):212-9. doi: 10.3988/jcn.2015.11.3.212
29. Siderowf A, McDermott M, Kieburtz K, et al. Test-retest reliability of the unified Parkinson's disease rating scale in patients with early Parkinson's disease: results from a multicenter clinical trial. *Mov Disord* 2002;17(4):758-63. doi: 10.1002/mds.10011
30. Landers MR, Durand C, Powell DS, et al. Development of a scale to assess avoidance behavior due to a fear of falling: the Fear of Falling Avoidance Behavior Questionnaire. *Phys Ther* 2011;91(8):1253-65. doi: 10.2522/ptj.20100304
31. Powell LE, Myers AM. The Activities-specific Balance Confidence (ABC) Scale. *J Gerontol A Biol Sci Med Sci* 1995;50A(1):M28-34.
32. Franchignoni F, Horak F, Godi M, et al. Using psychometric techniques to improve the Balance Evaluation Systems Test: the mini-BESTest. *J Rehabil Med* 2010;42(4):323-31. doi: 10.2340/16501977-0537
33. Dalrymple-Alford JC, MacAskill MR, Nakas CT, et al. The MoCA: well-suited screen for cognitive impairment in Parkinson disease. *Neurology* 2010;75(19):1717-25. doi: 10.1212/WNL.0b013e3181fc29c9

34. Tu QY, Jin H, Ding BR, et al. Reliability, validity, and optimal cutoff score of the montreal cognitive assessment (changsha version) in ischemic cerebrovascular disease patients of hunan province, china. *Dement Geriatr Cogn Dis Extra* 2013;3(1):25-36. doi: 10.1159/000346845
35. Sasco AJ, Paffenbarger RS, Jr., Gendre I, et al. The role of physical exercise in the occurrence of Parkinson's disease. *Arch Neurol* 1992;49(4):360-5.
36. Thacker EL, Chen H, Patel AV, et al. Recreational physical activity and risk of Parkinson's disease. *Mov Disord* 2008;23(1):69-74. doi: 10.1002/mds.21772
37. Xu Q, Park Y, Huang X, et al. Physical activities and future risk of Parkinson disease. *Neurology* 2010;75(4):341-8. doi: 10.1212/WNL.0b013e3181ea1597
38. Logroscino G, Sesso HD, Paffenbarger RS, Jr., et al. Physical activity and risk of Parkinson's disease: a prospective cohort study. *J Neurol Neurosurg Psychiatry* 2006;77(12):1318-22. doi: 10.1136/jnnp.2006.097170
39. Hirsch EC, Vyas S, Hunot S. Neuroinflammation in Parkinson's disease. *Parkinsonism Relat Disord* 2012;18 Suppl 1:S210-2. doi: 10.1016/S1353-8020(11)70065-7
40. Wang Q, Liu Y, Zhou J. Neuroinflammation in Parkinson's disease and its potential as therapeutic target. *Transl Neurodegener* 2015;4:19. doi: 10.1186/s40035-015-0042-0
41. Whitton PS. Inflammation as a causative factor in the aetiology of Parkinson's disease. *Br J Pharmacol* 2007;150(8):963-76. doi: 10.1038/sj.bjp.0707167
42. Zoladz JA, Majerczak J, Zeligowska E, et al. Moderate-intensity interval training increases serum brain-derived neurotrophic factor level and decreases inflammation in Parkinson's disease patients. *J Physiol Pharmacol* 2014;65(3):441-8.
43. Spielman LJ, Little JP, Klegeris A. Physical activity and exercise attenuate neuroinflammation in neurological diseases. *Brain Res Bull* 2016;125:19-29. doi: 10.1016/j.brainresbull.2016.03.012
44. Judge JO, Lindsey C, Underwood M, et al. Balance improvements in older women: effects of exercise training. *Phys Ther* 1993;73(4):254-62; discussion 63-5.
45. Pau M, Leban B, Collu G, et al. Effect of light and vigorous physical activity on balance and gait of older adults. *Arch Gerontol Geriatr* 2014;59(3):568-73. doi: 10.1016/j.archger.2014.07.008
46. Cavanaugh JT, Ellis TD, Earhart GM, et al. Toward Understanding Ambulatory Activity Decline in Parkinson Disease. *Phys Ther* 2015;95(8):1142-50. doi: 10.2522/ptj.20140498
47. Duncan RP, Leddy AL, Cavanaugh JT, et al. Detecting and predicting balance decline in Parkinson disease: a prospective cohort study. *J Parkinsons Dis* 2015;5(1):131-9. doi: 10.3233/JPD-140478
48. Kay MC, Carroll DD, Carlson SA, et al. Awareness and knowledge of the 2008 Physical Activity Guidelines for Americans. *J Phys Act Health* 2014;11(4):693-8. doi: 10.1123/jpah.2012-0171
49. Piercy KL, Troiano RP, Ballard RM, et al. The Physical Activity Guidelines for Americans. *JAMA* 2018 doi: 10.1001/jama.2018.14854
50. Katzmarzyk PT, Lee IM, Martin CK, et al. Epidemiology of Physical Activity and Exercise Training in the United States. *Prog Cardiovasc Dis* 2017;60(1):3-10. doi: 10.1016/j.pcad.2017.01.004
51. Dyrstad SM, Hansen BH, Holme IM, et al. Comparison of self-reported versus accelerometer-measured physical activity. *Med Sci Sports Exerc* 2014;46(1):99-106. doi: 10.1249/MSS.0b013e3182a0595f
52. Grimm EK, Swartz AM, Hart T, et al. Comparison of the IPAQ-Short Form and accelerometry predictions of physical activity in older adults. *J Aging Phys Act* 2012;20(1):64-79.
53. Tucker JM, Welk GJ, Beyler NK. Physical activity in U.S.: adults compliance with the Physical Activity Guidelines for Americans. *Am J Prev Med* 2011;40(4):454-61. doi: 10.1016/j.amepre.2010.12.016
54. Adams SA, Matthews CE, Ebbeling CB, et al. The effect of social desirability and social approval on self-reports of physical activity. *Am J Epidemiol* 2005;161(4):389-98. doi: 10.1093/aje/kwi054

CURRICULUM VITAE

Samantha Johnson

E-mail address: smjohnson1994@yahoo.com

Education

University of Nevada, Reno
B.S., Community Health Sciences - Kinesiology emphasis, May 2016

University of Nevada, Las Vegas
D.P.T., Physical Therapy, May 2019

Tyler Ormsby

E-mail address: 21tormsby@gmail.com

Education

Brigham Young University
B.S., Exercise Science, May 2013

Arizona State University
M.S., Health and Wellness, May 2016

University of Nevada, Las Vegas
D.P.T., Physical Therapy, May 2019