

5-11-2018

The Moderation Effect of BDNF Genotype and Self-Reported Habitual Physical Activity Levels on Age of Onset, Disease Progression, and Postural Instability in Parkinson's

Kyle Johnson
University of Nevada, Las Vegas

Danielle Salgo
University of Nevada, Las Vegas

Jessica Zorn
University of Nevada, Las Vegas

Follow this and additional works at: <https://digitalscholarship.unlv.edu/thesesdissertations>



Part of the [Physical Therapy Commons](#)

Repository Citation

Johnson, Kyle; Salgo, Danielle; and Zorn, Jessica, "The Moderation Effect of BDNF Genotype and Self-Reported Habitual Physical Activity Levels on Age of Onset, Disease Progression, and Postural Instability in Parkinson's" (2018). *UNLV Theses, Dissertations, Professional Papers, and Capstones*. 3552.
<http://dx.doi.org/10.34917/14944073>

This Dissertation is protected by copyright and/or related rights. It has been brought to you by Digital Scholarship@UNLV with permission from the rights-holder(s). You are free to use this Dissertation in any way that is permitted by the copyright and related rights legislation that applies to your use. For other uses you need to obtain permission from the rights-holder(s) directly, unless additional rights are indicated by a Creative Commons license in the record and/or on the work itself.

This Dissertation has been accepted for inclusion in UNLV Theses, Dissertations, Professional Papers, and Capstones by an authorized administrator of Digital Scholarship@UNLV. For more information, please contact digitalscholarship@unlv.edu.

THE MODERATION EFFECT OF BDNF GENOTYPE AND SELF-REPORTED HABITUAL PHYSICAL ACTIVITY
LEVELS ON AGE OF ONSET, DISEASE PROGRESSION, AND POSTURAL INSTABILITY IN PARKINSON'S
DISEASE

By

Kyle N. Johnson

Danielle C. Salgo

Jessica B. Zorn

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
The Graduate College

University of Nevada, Las Vegas
May 2018

Copyright by Kyle Johnson, Danielle Salgo, and Jessica Zorn, 2018

All Rights Reserved.

May 11, 2018

This doctoral project prepared by

Kyle N. Johnson

Danielle C. Salgo

Jessica B. Zorn

entitled

The Moderation Effect of BDNF Genotype and Self-Reported Habitual Physical Activity Levels on Age of Onset, Disease Progression, and Postural Instability in Parkinson's

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

Daniel Young, Ph.D.
Research Project Advisor

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

ABSTRACT

Background and Purpose: Brain-derived neurotrophic factor (BDNF) levels have been reported to play an important role in driving neuroprotection in people with neurologic disorders, and levels of BDNF are known to increase in response to physical activity. Moreover, the level of BDNF produced is also affected by BDNF genotype. It is not known, however, whether one's BDNF genotype interacts with physical activity throughout life to affect a neuroprotective response in people with Parkinson's disease (PD). Therefore, the purpose of this study was to determine if BDNF genotype interacts with lifetime self-reported physical activity levels to affect disease severity and progression as determined by measures of gait, balance, and PD motor function.

Methods: Included in the study were 28 individuals with idiopathic PD. DNA collected from buccal cells was used to determine BDNF genotype. Self-report measures included a modified version of the Lifetime Physical Activity Questionnaire (LPAQ), the Fear of Falling Avoidance Behavior Questionnaire (FFABQ), and the Activities-Specific Balance Confidence scale (ABC), as well as 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 observational assessment of motor function.

Results: There was not a significant interaction between BDNF genotype and self-reported history of physical activity on measures of gait and balance in individuals with PD. There was also no interaction between BDNF genotype and history of physical activity on age of PD onset or severity of disease.

Discussion: Preliminary results did not reveal any differential effects of BDNF genotype and history of physical activity effecting gait and balance, age of disease onset, or disease severity in individuals with PD. While all of the analyses are currently underpowered due to sample size, there were trends to indicate that there may be some validity to the original hypotheses. Data collection for this study is ongoing.

ACKNOWLEDGEMENTS

This research study was made possible by the UNLV Physical Therapy Department Student Opportunity Grant. The authors would like to thank Dr. Merrill Landers, PT, DPT, PhD for his mentorship as principal investigator of this study, Kathy Nagle for her assistance with recruitment, and the study participants for their time and willingness to be involved in data collection. The authors would also like to thank Drs. Szu-Ping Lee, Kai-Yu Ho, Jing Nong Liang and Daniel Young for their additional mentorship throughout this project.

TABLE OF CONTENTS

ABSTRACT.....	iii
ACKNOWLEDGEMENTS.....	iv
LIST OF TABLES.....	vi
LIST OF FIGURES.....	vii
INTRODUCTION.....	1
METHODS.....	4
Study Design	4
Sample Size Calculation	6
Participants	6
Data Analysis.....	7
RESULTS	9
DISCUSSION.....	17
CONCLUSION.....	21
REFERENCES.....	22
CURRICULUM VITAE.....	26

LIST OF TABLES

Table 1. Number of participants meeting CDC activity levels by BDNF genotype and life phase	9
Table 2. ABC scores with 95% CI for each life phase by level of activity	10
Table 3. Modified FFABQ scores with 95% CI for each life phase by level of activity	10
Table 4. MiniBESTest scores with 95% CI for each life phase by level of activity	11
Table 5. Descriptive statistics for the comparison of Val/Val and Met allele carriers for the ABC, mFFABQ, and the MiniBESTest.	11
Table 6. Numbers of participants with a fall history for each life phase by level of CDC activity	12
Table 7. Numbers of participants by Hoehn and Yahr stage for each life phase by level of CDC activity..	13
Table 8. Interaction p values and effect sizes for the ABC, mFFABQ, or MiniBESTest for the 2 (Val/Val and Val/Met or Met/Met) X 2 (CDC+ and CDC- for each life phase) ANCOVA.....	15
Table 9. Interaction p values and effect sizes for the MDS-UPDRS III for the 2 (Val/Val and Val/Met or Met/Met) X 2 (CDC+ and CDC- for each life phase) ANCOVA	16

LIST OF FIGURES

Figure 1. Data collection protocol.....	6
Figure 2. CONSORT flow diagram of participants' progress through study.....	7
Figure 3. MiniBESTest scores based on genotype and meeting CDC activity levels during the life phase of 20-30 years of age.....	14
Figure 4. MiniBESTest scores based on genotype and meeting CDC activity levels during the life phase of 30-39 years of age.....	15
Figure 5. Age of onset based on meeting CDC activity levels at each life phase	16

INTRODUCTION

Parkinson's disease (PD) is a progressive neurodegenerative disorder that results in motor deficits including the cardinal signs of bradykinesia, rigidity, resting tremors, and postural instability.¹ The death of neurons within the substantia nigra pars compacta (SNpc) is a notable feature of the pathology of PD.² Normally, the SNpc releases dopamine that is utilized by the basal ganglia to up-regulate motor patterns within the cortex.³ Progressive attrition of these dopaminergic neurons appears to be the predominant cause for many of the motor signs associated with the disease, although a majority of the brain is eventually affected.⁴

Physical activity is crucial in the treatment and prevention of PD. Regular moderate to vigorous aerobic exercise throughout life has been repeatedly shown in epidemiologic research to decrease the risk of developing PD,⁵⁻⁹ but the mechanism for this protection is not fully understood. One hypothesis is that these effects are mediated in part by physical activity-related increases in the production of brain-derived neurotrophic factor (BDNF).^{10,11} BDNF contributes to motor learning and sustained motor function possibly by promoting cell division or neuronal trafficking, regulating neuronal plasticity, and preventing premature neuronal cell death,^{11,12} including protection of dopaminergic neurons.^{13,14} High-intensity aerobic exercise increases BDNF immediately after just one bout¹⁵⁻¹⁸ and is associated with increased motor learning and declarative memory in healthy subjects,¹⁹ those with a history of stroke (CVA),²⁰⁻²³ those with Alzheimer's disease (AD),^{10,11,19,24} and those with PD.^{14,25,26}

An individual's specific BDNF genotype, however, mediates the amount of BDNF ultimately produced. A functional single nucleotide polymorphism (SNP) of this gene commonly exists in which the valine at position 66 of the BDNF precursor polypeptide is substituted for methionine, commonly known as the Val66Met polymorphism. The presence of this amino acid substitution ultimately decreases the amount

of BDNF that is produced.²⁵ In mice, the homozygous Val/Val genotype results in the greatest production of BDNF after cerebral ischemic infarct.²² In individuals with Alzheimer's disease, heterozygous Met carriers have higher rates of atrophy in the hippocampus over time, which is an AD-related marker of neurodegeneration.²⁷ In mice post-cerebral infarct, the homozygous Met/Met genotype results in the lowest average production of BDNF, shown to be less than half of their Val/Val counterparts at certain stages of recovery following cerebral ischemic infarct.²²

Initial studies suggest that this genetic polymorphism and aerobic activity levels may influence BDNF production simultaneously.^{12,21} For instance, subjects post-CVA with a Val/Val genotype had a better response to aerobic exercise and activities to promote motor learning than participants with the Met allele.²¹ While it appears unlikely that the Val66Met polymorphism alone affects the age of onset of PD,¹² it is possible that an interaction between BDNF genotype and history of physical activity may confer benefits for this population. However, no studies have investigated the effect of this interaction on PD onset and severity or on the level of function of individuals with PD. Therefore, the purpose of this study was to determine if BDNF genotype interacts with lifetime self-reported physical activity levels to affect the degree of disease severity as determined by measures of gait and postural stability, as well as age of onset in individuals with PD.

This study was shaped by two aims. Primary Aim 1 was to determine if there was an interaction between BDNF genotype and history of physical activity on measures of gait and postural stability in individuals with PD. We hypothesized that individuals with a homozygous Val/Val genotype and high levels of aerobic activity throughout the lifespan would have reduced disease severity as indicated by better gait and postural stability measures than other genotypes with similar or lower activity levels. Primary Aim 2 was to determine if there was an interaction between BDNF genotype and history of physical activity on

year of PD onset. We hypothesized that individuals with a homozygous Val/Val genotype and high levels of aerobic activity throughout the lifespan would be diagnosed later in life compared to the other BDNF genotypes with similar activity levels.

METHODS

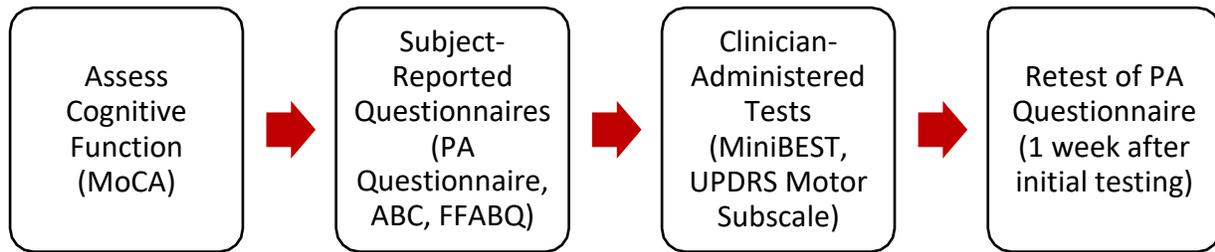
Study Design

A cross-sectional design was used for the study. BDNF genotype was determined using buccal cells and polymerase chain reaction (PCR). This method was preferred as it is quick, safe, non-invasive, and relatively inexpensive. Physical activity throughout the lifespan was measured using a modified version of the Lifetime Physical Activity Questionnaire (LPAQ) initially developed and validated by Chasan-Taber et al.²⁸ The questionnaire inquired 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.^{29,30} Additionally, we tested for reliability of our survey in people with PD by recruiting 15 (age= 64.3 years, SD= 4.9; males= 10, females= 5; Montreal Cognitive Assessment=27.2, SD=2.0; years since diagnosis=8.1, SD=5.5) of our participants to receive a second copy of the survey one week after initial testing either by e-mail or postal mail returned via a postage-paid envelope. An Intraclass Correlation Coefficient (ICC) model 3 showed moderate and vigorous physical activity recollection ranged from .77 to .91 for all of the time points between 20-29 years to 5 years before diagnosis. ICCs for walking and sitting were much more variable for the same time periods and ranged from .29 to .82. ICCs for the teen years were low: <.001 for moderate activity, .55 for vigorous, .07 for walking, and .49 for sitting. Likewise, ICCs were generally low for the time since diagnosis (all below .25) except for vigorous activity which was .91, suggesting that the reliability of the LPAQ was best for recollection of vigorous activity for every time point. Despite the small sample size, the reliability of the self-report questionnaire about lifetime physical activity levels in people with Parkinson's disease was

good for recollection of moderate and vigorous physical activity at almost all time points with vigorous activity having the most consistent test-retest reliability.

Gait and balance function was quantified using subject-reported measures, including the Fear of Falling Avoidance-Behavior Questionnaire (FFABQ)³¹ and the Activities-Specific Balance Confidence Scale (ABC),³² as well as a clinician-administered measure, the Mini-BESTest³³, all of which have been shown to have excellent inter-rater and intra-rater reliability and construct validity in the PD population. The ABC has excellent test-retest reliability (ICC=0.94)³⁴ and excellent internal consistency (Cronbach's alpha = 0.92-0.96)^{34,35} in individuals with PD. The ABC correlated with the FFABQ ($r = -0.68, p < 0.01$).³¹ The FFABQ has good test-retest reliability (ICC =0.81) and is valid in differentiating between elderly adults who fall and those who do not.³¹ The Mini-BESTest has excellent test-retest reliability (ICC = 0.92),³⁶ excellent concurrent validity with the Berg Balance Test,³⁷⁻³⁹ and excellent ability to detect balance deficits in Hoehn and Yahr stages 1-2 with superior disease severity detection to the Berg Balance Scale.³⁸ Disease severity was measured using the motor subscale (section 3) of the Movement Disorder Society – Unified Parkinson's Disease Rating Scale (MDS-UPDRS)⁴⁰ and the Hoehn & Yahr Scale. The Hoehn & Yahr Scale was selected since it shows stronger reliability and validity in categorizing the progression of PD than the Modified Hoehn & Yahr.⁴¹ 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 documented.⁴²⁻⁴⁴ Figure 1 below summarizes the data collection protocol followed for all participants in the study.

Figure 1. Data collection protocol



Sample Size Calculation

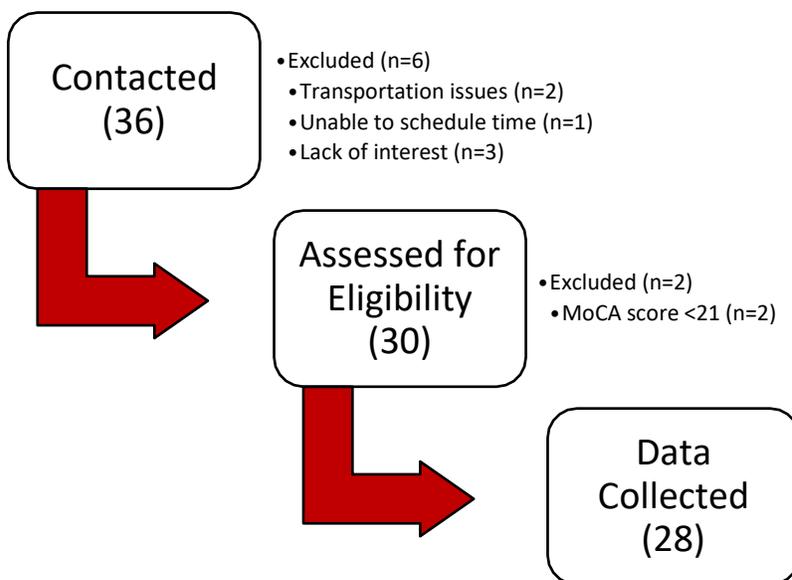
Sample size was estimated using PASS 14.0 (NCSS, LLC. Kaysville, Utah, USA, ncss.com/software/pass) for Aim 1. The sample size estimation was based on three factors at 3 (Val/Val, Val/Met, and Met/Met), 2 (Met CDC levels (CDC+) and did not meet CDC levels (CDC-)), and 4 levels (20s, 30s, 40s, and 50s) using a 3 X 3 X 4 factorial ANOVA with an alpha of .05 and power at 70%. This factorial design has 36 cells (treatment combinations). A total of 288 participants are required to provide 8 participants per cell with a within-cell standard deviation of 0.5 for a three-way interaction with an effect size of 0.4.

Participants

To be included, participants must have had neurologist-diagnosed idiopathic PD. Since there were several outcome measures that were self-report and required accurate recall, participants were excluded if they had cognitive impairment (scores <21) using the Montreal Cognitive Assessment (MoCA).⁴⁵ The MoCA has been shown to have excellent test-retest reliability with an ICC = 0.97 and good validity for the detection of mild cognitive impairment in people with PD.^{46,47} Demographic data collected from each participant included age, gender, years since diagnosis, fall history, Hoehn and Yahr stage, LEDD (levodopa equivalent daily dose), and time since last medication dosage. Recruitment included snowball strategies with participants and recruiting visits to a movement disorders neurologist's office, PD support groups, physical therapy clinics, and senior centers. Thirty individuals

with PD were enrolled in the study; however, two participants had MoCA scores lower than 21 and were excluded from the analysis. Thus, 28 participants met all of the inclusion/exclusion criteria (mean age = 66.4 ± 2.3 ; 21 males, 7 females; mean years since diagnosis = 8.9 ± 5.5 ; fallers = 14, non-fallers = 14; Hoehn and Yahr stage I = 4, II = 15, III = 7, IV = 2; LEDD = 670.4 ± 455.5 ; time since last medication = 3.3 ± 4.1 ; Val/Val = 16, Val/Met = 12, Met/Met = 0) (Figure 2).

Figure 2. CONSORT flow diagram of participants' progress through study.



Data Analysis

Because the proposed sample size was not achieved during the data collection period, the proposed analyses were amended accordingly. To test Primary Aim 1, we segregated the data based on genotype (Val/Val and Val/Met or Met/Met) and, using chi square analyses (Yates' continuity correction), we determined if there were differences in the proportions of self-report achievement of CDC levels of moderate to vigorous activity levels (CDC+ and CDC-) across each of the following life phases: 20s, 30s, 40s, 50s, 5 years preceding diagnosis, and since diagnosis. We also compared the levels of activity for

each life phase using an ANCOVA for the following gait and balance outcomes: ABC, mFFABQ, and miniBESTest. BDNF genotype was also compared using non-parametric Kruskal-Wallis test on the same three gait and balance outcomes. This was also conducted for BDNF genotype. Covariates entered into the analyses were age, years since diagnosis, and whether or not one had a Deep Brain Stimulator (DBS). LEDD and time since last medication dose were not included as the correlations were not sufficiently strong ($r < .400$). Chi square analyses were used to determine if there were proportional differences for fall history and Hoehn and Yahr stage based on achievement of CDC activity levels. Even though we were underpowered for the analyses, we conducted a factorial ANOVA to determine the effect size of the interaction to adjust the sample size as this is an ongoing trial. We conducted 2 (Val/Val and Val/Met or Met/Met) X 2 (CDC+ and CDC- for each of the aforementioned life phases) ANCOVAs on measures of gait and balance. For disease onset on Primary Aim 2, we compared the age of PD onset by BDNF genotype using non-parametric Mann-Whitney tests. We did the same for CDC activity levels at each life phase. For disease severity, we used the same factorial ANCOVA (2 (Val/Val and Val/Met or Met/Met) X 2 (CDC+ and CDC-)) on MDS-UPDRS III using the same covariates.

RESULTS

There were no statistically significant differences in the proportions meeting CDC activity criteria (CDC+ and CDC-) by BDNF genotype across each of the following life phases (20s, 30s, 40s, 50s, 5 years preceding diagnosis, since diagnosis) (Table 1).

Table 1. Number of participants meeting CDC activity levels by BDNF genotype and life phase.

	Val/Val	Val/Met or Met/Met	P value
20s	CDC+ ¹ = 15 CDC- ² = 1	CDC+ = 10 CDC- = 2	0.8
30s	CDC+ = 15 CDC- = 1	CDC+ = 11 CDC- = 1	1.0
40s	CDC+ = 13 CDC- = 3	CDC+ = 9 CDC- = 3	1.0
50s	CDC+ = 13 CDC- = 3	CDC+ = 9 CDC- = 3	1.0
5 years preceding	CDC+ = 13 CDC- = 3	CDC+ = 11 CDC- = 1	0.8
Since diagnosis	CDC+ = 13 CDC- = 3	CDC+ = 10 CDC- = 2	1.0

¹CDC+ value represents individuals meeting CDC activity levels.

²CDC- value represents individuals not meeting CDC activity levels.

There were no statistically significant differences in ABC scores across each of the life phases based on meeting CDC activity criteria, $p \geq .673$ (Table 2). Likewise, there were no differences for mFFABQ scores, $p \geq .648$ (Table 3) or for miniBESTest overall scores, $p \geq .119$ (Table 4) based on meeting CDC activity criteria.

Table 2. ABC scores with 95% CI for each life phase by level of activity.

	CDC+	CDC-	P value
20s	67.5 (56.1-79.0)	84.7 (51.1-118.5)	0.7
30s	68.2 (56.9-79.5)	84.6 (42.7-126.5)	0.7
40s	67.8 (55.3-80.4)	75.0 (50.1-100.0)	0.8
50s	67.8 (55.3-80.4)	75.0 (50.1-100.0)	0.8
5 years preceding	69.3 (57.1-81.6)	69.9 (35.6-104.2)	0.9
Since diagnosis	72.1 (59.9-84.3)	56.9 (28.1-85.6)	0.7

Table 3. Modified FFABQ scores with 95% CI for each life phase by level of activity.

	CDC+	CDC-	P value
20s	14.0 (8.8-19.2)	15.5 (0.2-30.9)	0.7
30s	14.3 (9.2-19.4)	13.2 (-5.8-32.1)	0.7
40s	14.6 (8.9-20.2)	12.8 (1.6-24.0)	0.6
50s	14.6 (8.9-20.2)	12.8 (1.6-24.0)	0.6
5 years preceding	14.5 (9.0-19.9)	12.5 (-2.8-27.8)	0.7
Since diagnosis	13.8 (8.2-19.4)	15.9 (2.8-29.0)	0.6

Table 4. MiniBESTest scores with 95% CI for each life phase by level of activity.

	CDC+	CDC-	P value
20s	21.8 (19.6-24.0)	21.4 (15.0-27.8)	0.16
30s	21.9 (19.7-24.0)	20.3 (12.5-28.2)	0.15
40s	21.8 (19.5-24.2)	21.5 (16.9-26.2)	0.16
50s	21.8 (19.5-24.2)	21.5 (16.9-26.2)	0.16
5 years preceding	22.2 (19.9-24.4)	19.2 (13.0-25.5)	0.12
Since diagnosis	22.1 (19.8-24.4)	20.1 (14.8-25.5)	0.14

There were no statistically significant differences between Val/Val and Met allele carriers on the ABC ($p=.458$), mFFABQ ($p=.692$), and minBESTest ($p=.469$) (Table 5). There were no statistically significant differences in fall history by CDC activity criteria at each life phase, $p \geq .185$ (Table 6). Likewise, there were no differences in Hoehn and Yahr proportions by CDC activity criteria for each life phase, $p \geq .427$ (Table 7).

Table 5. Descriptive statistics for the comparison of Val/Val and Met allele carriers for the ABC, mFFABQ, and the MiniBESTest.

	Genotype	Mean	Standard Deviation
ABC	Val/Val	68.5	22.6
	Val/Met	70.5	32.3
mFFABQ	Val/Val	13.8	9.6
	Val/Met	14.7	15.5
MiniBESTest	Val/Val	21.6	4.5
	Val/Met	21.9	6.9

Table 6. Numbers of participants with a fall history for each life phase by level of CDC activity.

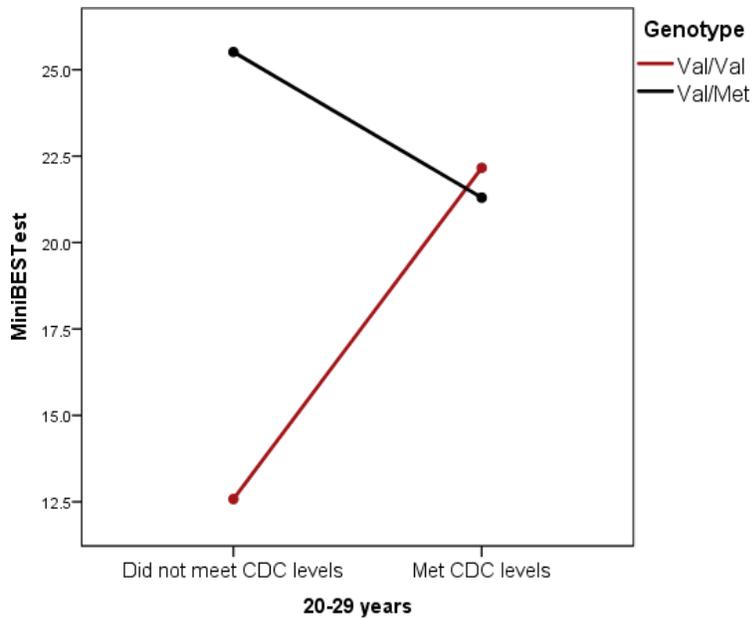
	CDC+		CDC-		P value
	Faller vs. Nonfaller	Injured vs. Noninjured Faller	Faller vs. Nonfaller	Injured vs Noninjured Faller	
20s	13:12	10:15	2:1	0:3	≥ 0.47
30s	13:13	10:16	1:1	0:2	≥ 0.74
40s	11:11	9:13	3:3	1:5	≥ 0.54
50s	11:11	9:13	3:3	1:5	≥ 0.54
5 years preceding	12:12	9:15	2:2	1:3	=1.00
Since diagnosis	11:12	10:13	3:2	0:5	≥ 0.19

Table 7. Numbers of participants by Hoehn and Yahr stage for each life phase by level of CDC activity.

	CDC+	CDC-	P value
20s			0.9
	3	0	
HY1	1	0	
HY1.5	15	2	
HY2	7	1	
HY3	2	0	
HY4			
30s			0.9
	3	0	
HY1	1	0	
HY1.5	14	1	
HY2	6	1	
HY3	2	0	
HY4			
40s			0.8
	2	1	
HY1	1	0	
HY1.5	12	3	
HY2	6	1	
HY3	1	1	
HY			
50s			0.8
	2	1	
HY1	1	0	
HY1.5	12	3	
HY2	6	1	
HY3	1	1	
HY			
5 years preceding			0.4
	2	1	
HY1	1	0	
HY1.5	14	1	
HY2	6	1	
HY3	1	1	
HY			
Since diagnosis			0.7
	3	0	
HY1	1	0	
HY1.5	11	4	
HY2	6	1	
HY3	2	0	
HY4			

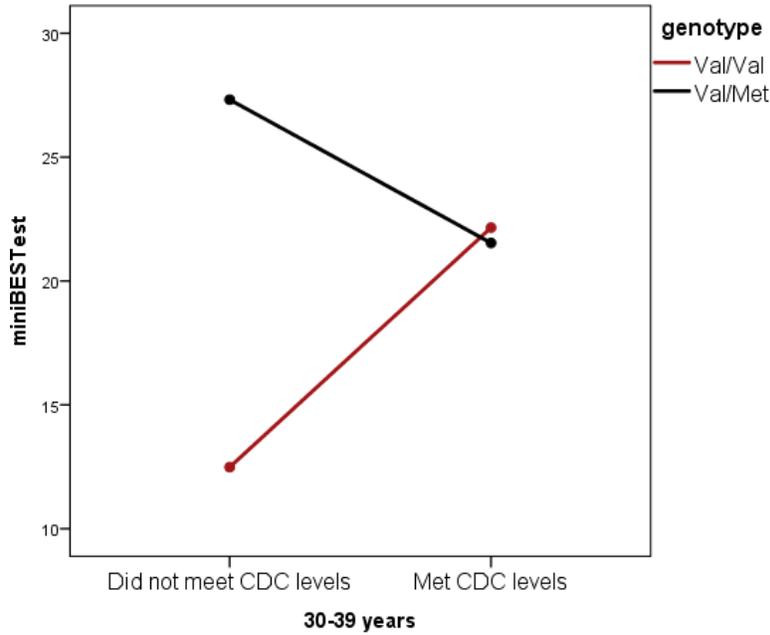
There were no statistically significant interactions for the ABC, mFFABQ, or miniBESTest for the 2 (Val/Val and Val/Met or Met/Met) X 2 (CDC+ and CDC-) ANCOVAs (covariates entered: age, years since diagnosis, and DBS status) during the 20s ($p \geq .112$, Figure 3 for miniBESTest), 30s ($p \geq .109$, Figure 4 for miniBESTest), 40s ($p \geq .316$), 50s ($p \geq .316$), 5 years before ($p \geq .318$), and since diagnosis ($p \geq .243$) (Table 8).

Figure 3. MiniBESTest scores based on genotype and meeting CDC activity levels during the life phase of 20-30 years of age.



Covariates appearing in the model are evaluated at the following values: Age = 66.43, Years since Dx = 8.89, DBS? = 1.18

Figure 4. MiniBESTest scores based on genotype and meeting CDC activity levels during the life phase of 30-39 years of age.



Covariates appearing in the model are evaluated at the following values: Age = 66.43, Years since Dx = 8.89, DBS? = 1.18

Table 8. Interaction p values and effect sizes for the ABC, mFFABQ, or MiniBESTest for the 2 (Val/Val and Val/Met or Met/Met) X 2 (CDC+ and CDC- for each life phase) ANCOVA.

	ABC		mFFABQ		miniBESTest	
	Interaction p value	Partial eta squared	Interaction p value	Partial eta squared	Interaction p value	Partial eta squared
20s	0.848	0.110	0.721	0.148	0.112	0.363
30s	0.891	0.095	0.582	0.186	0.109	0.365
40s	0.937	0.076	0.813	0.121	0.316	0.265
50s	0.937	0.076	0.813	0.121	0.316	0.265
5 years preceding	0.973	0.054	0.801	0.125	0.318	0.264
Since diagnosis	0.518	0.203	0.393	0.240	0.243	0.293

Year of diagnosis was not statistically different between the two genotypes, $p=.275$. Likewise, there were no statistically significant differences for age of onset based on CDC activity levels at 20s ($p=.457$), 30s ($p=.964$), 40s ($p=.866$), 50s ($p=.866$), 5 years preceding ($p=.139$), and since diagnosis ($p=.082$) (Figure 5). There were no statistically significant interactions for disease severity (MDS-UPDRS III), $p \geq .272$ (Table 9).

Figure 5. Age of onset based on meeting CDC activity levels at each life phase.

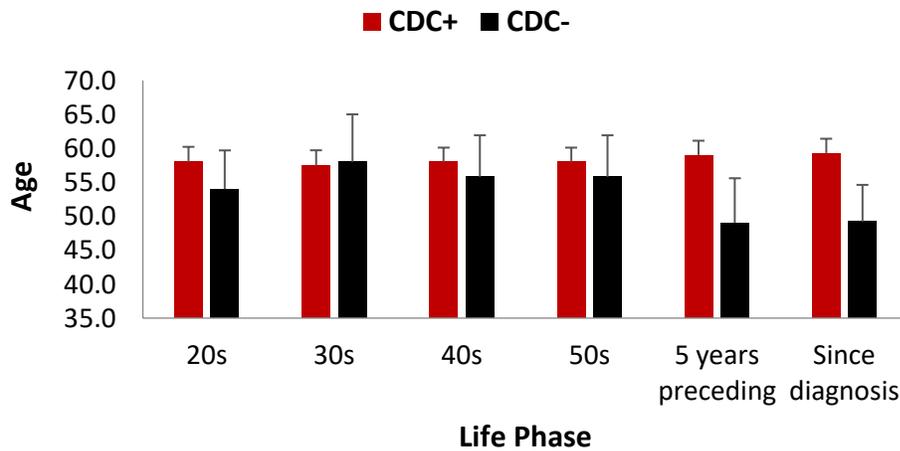


Table 9. Interaction p values and effect sizes for the MDS-UPDRS III for the 2 (Val/Val and Val/Met or Met/Met) X 2 (CDC+ and CDC- for each life phase) ANCOVA.

	ABC	
	Interaction p value	Partial eta squared
20s	0.370	0.247
30s	0.453	0.222
40s	0.357	0.251
50s	0.357	0.251
5 years preceding	0.272	0.281
Since diagnosis	0.325	0.262

DISCUSSION

There were no statistically significant differences in the subject proportions meeting CDC activity criteria by BDNF genotype across each life phase. There were no statistically significant differences in ABC, mFFABQ, or miniBESTest scores for each life phase based on meeting CDC activity criteria. Val/Val allele carriers did not score significantly differently on the ABC, mFFABQ, or miniBESTest than their Met allele-carrying counterparts. Likewise, they did not show significant differences in fall history, Hoehn and Yahr proportions, age of onset, or disease severity. From these results, it cannot be concluded that BDNF genotype interacts with lifetime self-reported physical activity levels to affect the degree of disease severity and age of onset in individuals with PD.

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 CDC recommendations for physical activity at all stages of their lives (Table 1). In comparison, only 51% of adults in the United States report meeting CDC guidelines for aerobic exercise.⁴⁸ Additionally, adults tend to over-estimate their time engaging in exercise. 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 actually met the guidelines as measured by accelerometer, a pattern that was consistent at all age groups (20s, 30s, 40s, 50s, 60s, >70).⁴⁹ Thus, it is possible that participants in this study also overestimated their physical activity levels.

The nature and recruitment strategy used in this study may have encouraged even higher incidences of over-reporting physical activity. Participants were told they were participating in a study about the relationship between physical activity and disease progression. It is possible some unconsciously over-estimated their past exercise, believing it to be a possible modifiable risk factor for their current health

status. There may have also been response bias among participants to make themselves appear more active as participants were not told the researchers would be blinded to their responses. Alternatively, those agreeing to volunteer for the study may have been motivated to do so because they had a high level of past and/or current physical activity; thus, they may not be a true representative sample of the PD population. A larger sample size or alternative recruiting strategies to target individuals with PD who are less likely to participate in research studies may mitigate these possible effects.

Despite the high number of participants reporting having met CDC recommended levels of physical activity throughout their lives, descriptive statistics and initial data analysis showed little difference between the Val/Val and Met carriers in the number of participants who reported meeting/not meeting CDC recommended levels of physical activity ($p > 0.8$) (Table 1). Likewise, there was little difference in measures of gait and balance including the ABC, FFABQ, and miniBEST between participants reporting to have met or not met CDC guidelines of physical activity at each stage of life (Tables 2-4). The difference between the mean scores of the three outcome measures (ABC, FFABQ, and miniBEST) was also within the standard of error regardless of the participants' genotypes (Table 5). Additionally, participants who had or had not met CDC recommended levels of physical activity demonstrated no difference in fall history ($p \geq 0.185$) (Table 6) or differences in Hoehn and Yahr scores (Table 7). This is consistent with our hypothesis that levels of physical activity or BDNF genotype individually are not sufficient to affect measures of gait and balance or disease severity in individuals with PD although the study is currently underpowered.

Even though the aforementioned results were largely consistent between groups, one note-worthy difference was between the Met carriers and Val/Val participants 5 years prior to diagnosis when looking at the ABC. There was no statistically significant interaction between the ABC, mFFABQ, or the

miniBEST with regards to participants' age, years since diagnosis, and DBS status (Table 8). However, the combination of BDNF genotype and CDC recommended level of aerobic exercise during the 5 years prior to diagnosis tended to affect ABC scores ($p = 0.272$) more than other outcome measures, although the interaction is not considered significant at this time (Table 9). If this trend continues with a larger sample, there may be a correlation between physical activity and the prodromal stage of PD depending on BDNF genotype. Future research may benefit from looking at the desire or ability to exercise during this prodromal stage in individuals who are Met allele carriers compared to their homozygous counterparts pending verification of these early patterns in data.

An interesting trend also appeared at the ages of 20-29 years and 30-39 years with the miniBEST (Fig 3-4). Participants who were Val/Met and reported not meeting CDC activity criteria actually had higher average miniBEST scores than their same genotypic counterparts who reported meeting CDC activity criteria. In contrast, participants with the Val/Val genotype and reported not meeting the CDC levels for activity performed worse on the miniBEST than their same genotypic counterparts who reported meeting CDC recommended physical activity levels. If this trend continues with a larger sample size, this may indicate that individuals with the homozygous Val/Val BDNF genotype may benefit more from aerobic exercise during their 20s to 40s than individuals with the heterozygous Val/Met genotype to improve balance and gait after they are diagnosed with PD. If correct, this could strengthen the argument for BDNF genetic testing and prescribing aerobic exercise for individuals who are Val/Val and at increased risk for being diagnosed with PD in the future.

Age of onset also presented some remarkable trends despite being underpowered. Participants who reported having met CDC recommended levels of activity at each phase of life tended to have a later diagnosis of PD than participants who reported not having met CDC recommended activity levels (Fig. 5). This is consistent with previous studies that demonstrate physical activity may be a modifiable risk

factor for the diagnosis of PD.⁵⁻⁹ If this trend continues as research progresses, it may demonstrate that exercise not only lowers the chance of being diagnosed with PD, but also delays its onset, which would be a novel finding.

Despite some interesting initial trends in the data, at this early stage in research, we cannot confirm whether or not measures of gait and balance or age of onset of PD are correlated with BDNF genotype and physical activity. This correlation would require a larger sample size due to the high number of factors that have been shown to be correlated with PD,^{5,50,51} and therefore, may have different disease etiologies and progressions which were not captured in this study.

The primary limitation to our study is a small sample size. MiniBESTest scores in relation to lifetime self-reported history of physical activity had the strongest trend toward significance with $p < 0.162$ (Table 4). Using the effect sizes from Table 8 ranging from 0.262-0.365, the necessary sample size to achieve significance was estimated to be from 32 to 197 participants, which is greater than the number in the current study. Other limitations to our study include the reliability of the novel LPAQ that was used to quantify physical activity over lifespan as previously discussed. The nature of self-reported data is inherently less reliable than objective measures, and faults in recall may increase with participant age or cognitive decline short of dementia. All tests were performed in accordance with published protocols. As previously mentioned, 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 sample recruitment biases.

CONCLUSION

In conclusion, our results do not indicate a significant relationship between BDNF genotype and lifetime history of physical activity at this time. Likewise, these early results do not support a link between age of onset, disease severity, or postural instability in PD. Participants in our sample with the Val/Val polymorphism and high levels of lifetime physical activity do not present with significantly later onset, lesser severity, or higher postural instability than their heterozygous Val/Met counterparts. These results should be considered preliminary at this time due to being underpowered and will be reevaluated when an adequate sample has been tested. Data collection is currently on-going. The validity and reliability of the LPAQ will also continue to be investigated with a larger sample size to determine the role of lifetime physical activity and its relationship to BDNF genotype and disease progression. Significance on this measure may shed light on the need for more objective physical activity measurements at certain time points in individual's lives either before or after being diagnosed with PD to better understand the influence of genetics on disease trajectory.

REFERENCES

1. Jankovic J. Parkinson's disease: clinical features and diagnosis. *J Neurol Neurosurg Psychiatry*. 2008;79(4):368-376. doi:10.1136/jnnp.2007.131045.
2. Pearson-Fuhrhop KM, Minton B, Acevedo D, Shahbaba B, Cramer SC. Genetic variation in the human brain dopamine system influences motor learning and its modulation by L-Dopa. *PLoS One*. 2013;8(4):e61197. doi:10.1371/journal.pone.0061197.
3. Baquet ZC. Brain-Derived Neurotrophic Factor Is Required for the Establishment of the Proper Number of Dopaminergic Neurons in the Substantia Nigra Pars Compacta. *J Neurosci*. 2005;25(26):6251-6259. doi:10.1523/JNEUROSCI.4601-04.2005.
4. Calabresi P, Picconi B, Parnetti L, Di Filippo M. A convergent model for cognitive dysfunctions in Parkinson's disease: the critical dopamine–acetylcholine synaptic balance. *Lancet Neurol*. 2006;5(11):974-983. doi:10.1016/S1474-4422(06)70600-7.
5. 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):328-333. doi:10.1016/S0303-8467(02)00027-6.
6. Yang F, Trolle Lagerros Y, Bellocco R, et al. Physical activity and risk of Parkinson's disease in the Swedish National March Cohort. *Brain*. 2014;138(2):269-275. doi:10.1093/brain/awu323.
7. Sääksjärvi K, Knekt P, Männistö 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. doi:10.1007/s10654-014-9887-2.
8. Chen H, Zhang SM, Schwarzschild M, Hernán M, Ascherio. Physical activity and the risk of Parkinson disease. *Neurology*. 2005;64(4):664-669. doi:10.1212/01.WNL.0000151960.28687.93.
9. Xu Q, Park Y, Huang X, et al. Physical activities and future risk of Parkinson disease. *Neurology*. 2010. doi:10.1212/WNL.0b013e3181ea1597.
10. Coelho FG de M, Vital TM, Stein AM, et al. Acute aerobic exercise increases brain-derived neurotrophic factor levels in elderly with Alzheimer's disease. *J Alzheimers Dis*. 2014;39(2):401-408. doi:10.3233/JAD-131073.
11. Nascimento CMC, 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). doi:10.3233/JAD-140576.
12. Hong C-J, Liu H-C, Liu T-Y, Lin C-H, Cheng C-Y, Tsai S-J. Brain-derived neurotrophic factor (BDNF) Val66Met polymorphisms in Parkinson's disease and age of onset. *Neurosci Lett*. 2003;353. doi:10.1016/j.neulet.2003.09.009.
13. Ahlskog JE. Does vigorous exercise have a neuroprotective effect in Parkinson disease? *Neurology*. 2011;77(3):288-294. doi:10.1212/WNL.0b013e318225ab66.
14. 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). doi:10.1111/j.1468-1331.2009.02706.x.

15. Mang CS, Campbell KL, Ross CJD, Boyd L a. 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):1707-1716. doi:10.2522/ptj.20130053.
16. Skriver K, Roig M, Lundbye-Jensen J, et al. Acute exercise improves motor memory: exploring potential biomarkers. *Neurobiol LearnMem.* 2014;116:46-58. doi:10.1016/j.nlm.2014.08.004.
17. Nanda B, Balde J, Manjunatha S. The Acute Effects of a Single Bout of Moderate-intensity Aerobic Exercise on Cognitive Functions in Healthy Adult Males. *J Clin Diagn Res.* 2013;7(9):1883-1885. doi:10.7860/JCDR/2013/5855.3341.
18. Vaynman S, Ying Z, Gomez-Pinilla F. Hippocampal BDNF mediates the efficacy of exercise on synaptic plasticity and cognition. *Eur J Neurosci.* 2004;20(10):2580-2590. doi:10.1111/j.1460-9568.2004.03720.x.
19. Smith AE, Goldsworthy MR, Garside T, Wood FM, Ridding MC. The influence of a single bout of aerobic exercise on short-interval intracortical excitability. *Exp Brain Res.* 2014;232(6):1875-1882. doi:10.1007/s00221-014-3879-z.
20. Helm EE, Tyrell CM, Pohlig RT, Brady LD, Reisman DS. The presence of a single-nucleotide polymorphism in the BDNF gene affects the rate of locomotor adaptation after stroke. *Exp Brain Res.* 2016;234(2):341-351. doi:10.1007/s00221-015-4465-8.
21. Di Lazzaro V, Pellegrino G, Di Pino G, et al. Val66Met BDNF gene polymorphism influences human motor cortex plasticity in acute stroke. *Brain Stimul.* 8(1):92-96. doi:10.1016/j.brs.2014.08.006.
22. Qin L, Kim E, Ratan R, Lee FS, Cho S. Genetic variant of BDNF (Val66Met) polymorphism attenuates stroke-induced angiogenic responses by enhancing anti-angiogenic mediator CD36 expression. *J Neurosci.* 2011;31(2):775-783. doi:10.1523/JNEUROSCI.4547-10.2011.
23. Mang CS, Campbell KL, Ross CJD, Boyd L a. Perspective Promoting Neuroplasticity for Motor Rehabilitation After Stroke : Considering the Effects of Aerobic Brain-Derived Neurotrophic Factor. *Phys Ther.* 2013;93:1707-1716. doi:10.2522/ptj.20130053.
24. Honea RA, Cruchaga C, Perea RD, et al. Characterizing the Role of Brain Derived Neurotrophic Factor Genetic Variation in Alzheimer's Disease Neurodegeneration. Ginsberg SD, ed. *PLoS One.* 2013;8(9):e76001. doi:10.1371/journal.pone.0076001.
25. Altmann V, Schumacher-Schuh AF, Rieck M, Callegari-Jacques SM, Rieder CRM, Hutz MH. Val66Met BDNF polymorphism is associated with Parkinson's disease cognitive impairment. *Neurosci Lett.* 2016. doi:10.1016/j.neulet.2016.01.030.
26. Bialecka M, Kurzawski M, Roszmann A, et al. BDNF G196A (Val66Met) polymorphism associated with cognitive impairment in Parkinson's disease. *Neurosci Lett.* 2014;561. doi:10.1016/j.neulet.2013.12.051.
27. Honea RA, Cruchaga C, Perea RD, et al. Characterizing the Role of Brain Derived Neurotrophic Factor Genetic Variation in Alzheimer's Disease Neurodegeneration , For the Alzheimer's Disease Neuroimaging Initiative (ADNI). doi:10.1371/journal.pone.0076001.
28. Chasan-Taber L. Reproducibility of a Self-administered Lifetime Physical Activity Questionnaire among Female College Alumnae. *Am J Epidemiol.* 2002;155(3):282-291. doi:10.1093/aje/155.3.282.

29. Friedenreich CM, Courneya KS, Bryant HE. The lifetime total physical activity questionnaire: development and reliability. *Med Sci Sports Exerc.* 1998;30(2):266-274.
30. De Vera MA, Ratzlaff C, Doerfling P, Kopec J. Reliability and validity of an internet-based questionnaire measuring lifetime physical activity. *Am J Epidemiol.* 2010;172(10):1190-1198. doi:10.1093/aje/kwq273.
31. Landers MR, Durand C, Powell DS, Dibble LE, Young DL. 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):1253-1265. doi:10.2522/ptj.20100304.
32. Powell LE, Myers AM. The Activities-specific Balance Confidence (ABC) Scale. *J Gerontol A Biol Sci Med Sci.* 1995;50A(1):M28-34. doi:10.1007/SpringerReference_6342.
33. Franchignoni F, Horak F, Godi M, Nardone A, Giordano A. Using psychometric techniques to improve the balance evaluation systems test: The mini-bestest. *J Rehabil Med.* 2010;42(4):323-331. doi:10.2340/16501977-0537.
34. Steffen T, Seney M. Test-Retest Reliability and Minimal Detectable Change on Balance and Ambulation Tests, the 36-Item Short-Form Health Survey, and the Unified Parkinson Disease Rating Scale in People With Parkinsonism. *Phys Ther.* 2008;88(6):733-746. doi:10.2522/ptj.20070214.
35. Dal Bello-Haas V, Klassen L, Sheppard MS, Metcalfe A. Psychometric Properties of Activity, Self-Efficacy, and Quality-of-Life Measures in Individuals with Parkinson Disease. *Physiother Canada.* 2011;63(1):47-57. doi:10.3138/ptc.2009-08.
36. Leddy AL, Crouner BE, Earhart GM. Utility of the Mini-BESTest, BESTest, and BESTest Sections for Balance Assessments in Individuals With Parkinson Disease. *J Neurol Phys Ther.* 2011;35(2):90-97. doi:10.1097/NPT.0b013e31821a620c.
37. McNeely ME, Duncan RP, Earhart GM. Medication improves balance and complex gait performance in Parkinson disease. *Gait Posture.* 2012;36(1):144-148. doi:10.1016/j.gaitpost.2012.02.009.
38. King LA, Priest KC, Salarian A, Pierce D, Horak FB. Comparing the Mini-BESTest with the Berg Balance Scale to Evaluate Balance Disorders in Parkinson's Disease. *Parkinsons Dis.* 2012;2012:1-7. doi:10.1155/2012/375419.
39. Bergström M, Lenholm E, Franzén E. Translation and validation of the Swedish version of the mini-BESTest in subjects with Parkinson's disease or stroke: A pilot study. *Physiother Theory Pract.* 2012;28(7):509-514. doi:10.3109/09593985.2011.653707.
40. Goetz CG, Tilley BC, Shaftman SR, et al. Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): Scale presentation and clinimetric testing results. *Mov Disord.* 2008;23(15):2129-2170. doi:10.1002/mds.22340.
41. 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):1020-1028. doi:10.1002/mds.20213.
42. Martinez-Martin P, Gil-Nagel A, Gracia LM, et al. Unified Parkinson's disease rating scale characteristics and structure. *Mov Disord.* 1994;9(1):76-83. doi:10.1002/mds.870090112.

43. Richards M, Marder K, Cote L, Mayeux R. Interrater reliability of the Unified Parkinson's Disease Rating Scale motor examination. *Mov Disord*. 1994;9(1):89-91. doi:10.1002/mds.870090114.
44. Siderowf A, McDermott M, Kieburtz K, Blindauer K, Plumb S, Shoulson I. 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):758-763. doi:10.1002/mds.10011.
45. Ziad S, Nasreddine NAP, Be'dirian V, Simon Charbonneau VW, Isabelle Collin, Jeffrey L. Cummings HC. The Montreal Cognitive Assessment, MoCA: A brief screening tool for mild cognitive impairment. *Am Geriatr*. 2005;53(4):695-699. doi:10.1111/j.1532-5415.2005.53221.x.
46. 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):1738-1745. doi:10.1212/WNL.0b013e3181c34b47.
47. Tu Q-Y, Jin H, Ding B-R, 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.
48. Katzmarzyk PT, Lee I-M, Martin CK, Blair SN. Epidemiology of Physical Activity and Exercise Training in the United States. *Prog Cardiovasc Dis*. 2017. doi:10.1016/j.pcad.2017.01.004.
49. Tucker JM, Welk GJ, Beyler NK. Physical Activity in U.S. Adults. *Am J Prev Med*. 2011;40(4):454-461. doi:10.1016/j.amepre.2010.12.016.
50. Priyadarshi A, Khuder SA, Schaub EA, Priyadarshi SS. Environmental Risk Factors and Parkinson's Disease: A Metaanalysis. *Environ Res*. 2001;86(2):122-127. doi:10.1006/enrs.2001.4264.
51. Pringsheim T, Jette N, Frolkis A, Steeves TDL. The prevalence of Parkinson's disease: A systematic review and meta-analysis. *Mov Disord*. 2014;29(13):1583-1590. doi:10.1002/mds.25945.

CURRICULUM VITAE

Jessica B. Zorn

(701) 720-1074

E-mail address: jbzorn@gmail.com

Education

Colorado State University

B.S., Biological Sciences, May 2007

University of Nevada, Las Vegas

D.P.T., Physical Therapy, May 2018

Kyle N. Johnson

602-689-6519

E-mail address: kylenj527@gmail.com

Education

Arizona State University

B.S., Biological Sciences, May 2015

University of Nevada, Las Vegas

D.P.T., Physical Therapy, May 2018

E-mail address: daniellesalgo@gmail.com

Education

University of Nevada Reno
B.S., Biology, May 2014

University of Nevada, Las Vegas
D.P.T., Physical Therapy, May 2018