ABSTRACT

THE ASSOCIATIONS BETWEEN HABITUAL PHYSICAL ACTIVITY LEVELS AND SERUM BRAIN-DERIVED NEUROTROPHIC FACTOR (BDNF) LEVELS IN OLDER ADULTS

by Caitlyn Taylor Picard

The primary purpose of this study was to assess the relationship between habitual physical activity levels and serum-BDNF levels in older adults. A convenient blood serum sample set of 68 subjects had valid baseline data for body mass index (BMI), body composition, amount of moderate and vigorous physical activity (MVPA), and 7-day accelerometer data. The blood serum was stored at -80 degrees Celsius until it was analyzed for BDNF levels using an ELISA. Subject data reflected a range from 18.7 to 136.3 minutes per day of moderate to vigorous physical activity. Objectively measured PA was not significantly correlated with serum-BDNF levels. Body fat percentage was positively correlated with serum-BDNF levels ($p \leq 0.05$). However, when controlling for sex, there were no significant correlations. These results present the need for further analysis of the sex differences in BDNF levels.

THE ASSOCIATIONS BETWEEN HABITUAL PHYSICAL ACTIVITY LEVELS AND SERUM BRAIN-DERIVED NEUROTROPHIC FACTOR (BDNF) LEVELS IN OLDER ADULTS

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by

Caitlyn Taylor Picard

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Advisor: Kyle Timmerman, PhD, FACSM

Reader: Kevin Ballard, PhD, FACSM

Reader: Helaine Alessio, PhD

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Department of Kinesiology, Nutrition, and Health

_____

Kyle Timmerman, PhD

_____

Kevin Ballard, PhD

_____

Helaine Alessio, PhD

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Chapter I

Introduction:

In the United States, one in three older adults will die from a form of Alzheimer's Disease or dementia. Five million Americans currently have Alzheimer's Disease (AD), making it the sixth leading cause of death in the United States (Alzheimer's Association, 2020). The direct cost to Americans caring for those with AD, totals an estimated $305 billion dollars, with 67% of that being paid for by Medicare and Medicaid programs. Thus, it is important to identify lifestyle factors that may attenuate the risk of dementia and AD in older adults. One such lifestyle factor may be physical activity.

Several studies have shown that physical activity can reduce the risk of AD at varying exercise modes and intensities. Specifically, studies have shown that low levels of physical activity are the highest risk factor for dementia and AD (Dahana, 2019; Norton, 2014, Szuhany, 2015). In a representative longitudinal study with adults over 65 was conducted in 2019, where they specified five healthy lifestyle behaviors that can mitigate the risks of AD (Dahana, 2019). The five healthy lifestyle behaviors are as follows: 150 minutes of moderate to vigorous physical activity per week, smoking status, participation in late-life cognitive activities, alcohol intake, and participation in the Mediterranean diet. Individuals were randomly selected for detailed assessments of incident AD, neurologic examinations, and cognitive performance testing for the clinical diagnosis of AD over 18 years. The subjects that participated in two to three of these activities, compared to zero to one, saw a 37% decreased risk of AD. The subjects that participated in four to five of these activities, compared to zero to one, saw a 60% decreased risk of AD. Therefore, it is important that older adults increase their exercise levels and other healthy behaviors to mitigate that risk.

While studies suggest that physical activity may modulate the risk of dementia, the precise mechanism underlying this connection is not fully understood. One proposed mechanism for cognitive enhancement due to exercise is Brain-Derived Neurotrophic Factor (BDNF). BDNF is a protein involved in neuronal growth, repair, and plasticity, which is essential for memory (Mori, 2021). BDNF is primarily produced in the hippocampus, amygdala, and cerebral cortex, and can pass the blood-brain barrier. BDNF's receptor, Tropomyosin related kinase B (TrkB), can be found in the cerebral cortex, hippocampus, thalamus, cerebellum, brain stem, spinal cord, and dorsal root ganglia, making it more difficult to analyze.

The gold standard measurement of BDNF would be through CNS samples, however, those are not readily available. Because BDNF can cross the blood-brain barrier, many have studied how accurately blood-serum samples can measure the levels of BDNF from the CNS. A few animal and human studies have shown significant moderately positive correlations between CNS BDNF and serum-BNDF samples (Klein, 2011; Mori, 2021). Klein found significant positive correlations between serum BDNF and hippocampal brain BDNF levels in rats ($r=0.66$, $p<0.05$) and pigs ($r=0.64$, $p<0.05$), but was unable to find a positive correlation in the mouse models (Klein, 2011). Mori, et al conducted a study in 2021 to verify BDNF serum levels with cerebrospinal fluid (CSF) BDNF levels in humans. In this study, the serum and CSF fluid samples were taken at the same time. They found that serum BDNF levels were moderately correlated with CSF levels ($r=0.49$, $p=0.005$) (Mori, 2021). Thus, blood serum-BDNF levels can be utilized as surrogate BDNF from non-invasive antecubital blood venipuncture.

Due to BDNF being a proposed mechanism for the benefits of physical activity to AD, many have studied the direct effects of physical activity on BDNF levels. By gaining information about how BDNF levels can be manipulated through exercise interventions, it can help us to better understand the effects of habitual physical activity levels on BDNF. Several studies have shown the effects of exercise dose and intensity on serum-BDNF levels (Mackay, 2017; Glud, 2019;). Mackay, et al found that an increase in habitual exercise when performed 4-7 times per week showed a significant increase in serum-BDNF levels, whereas 2-3 times per week did not (2017). These studies are important in understanding the effects that dose and intensity of exercise prescriptions can have on BDNF.

Since health benefits from physical activity have been shown, many have studied the effects of habitual physical activity on serum-BDNF levels (Beltran-Valls, 2018; Engeroff, 2018; Babaei, 2014; Hakansson, 2016; Maas, 2016). However, the results are conflicting. A cross-sectional study analyzed 234 adolescent male and female participants and found no significant correlations between objectively measured habitual physical activity and serum-BDNF levels (Beltran-Valls, 2018). Their reported range of total physical activity minutes per day ranged from 200.8 to 349.2 (Beltran-Valls, 2018). However, another study using 50 healthy older adults found a significant positive correlation between moderate to vigorous objectively measured physical activity and BDNF-serum levels (Engeroff, 2018). Their reported range of total physical activity minutes per day ranged from 147.0 to 279.3.

BDNF serum levels have been correlated with many inflammatory markers and anti-inflammatory markers (Jeenger, 2018; Tait, 2019). Several have researched the relationship between serum-BDNF levels and serum-CRP levels in subjects with depressive disorders. They found that patients with depressive disorders had significantly lower levels of BDNF-serum, but they did not find a relationship between the healthy group and depressive group for CRP levels (Soloey-Nilsen, 2022; Jeenger, 2018). All of these studies have observed the relationship between CRP levels and a cognitive measure, but to our knowledge, no studies have been conducted to see the relationship between BDNF and CRP levels in blood serum. BDNF levels have a very wide range of effects on the body and gaining an understanding of inflammatory markers in addition to BDNF serum levels will help our study gain a better understanding of our subjects' conditions.

The current literature is largely based on samples of healthy adolescents and middle-aged people. The lack of evaluation of older adults, who are at a higher risk of AD and dementia leaves a critical gap in the literature. In addition to the health differences, there are limited current publications with information on habitual exercise implications for older adults using objective measurements to assess the subject’s habitual exercise levels, with subject numbers over 50. Thus, the primary purpose of this study is to examine the associations between serum-BDNF levels and objective habitual physical activity levels in a relatively larger data set of older adults. The secondary purpose of the study is to examine the relationships between serum-BDNF levels and various other health values such as CRP serum levels and body composition data. We hypothesize that there will be a positive correlation between habitual physical activity levels and serum-BDNF levels in older adults.

Chapter II

Methods:

Study Design

The research design utilized in this study was a quantitative associational study. The convenient sample of 68 subjects had valid baseline data for body mass index (BMI), body composition, amount of moderate and vigorous physical activity (MVPA), and 7-day accelerometer data. The independent variables for this study are habitual physical activity level, BMI, body composition, and sex. The dependent variables are blood serum BDNF levels and CRP levels. The subjects have a wide spread of habitual physical activity levels which will allow for associational comparisons between serum BDNF levels and activity levels.

Subject Population

The 68 subjects consisted of men and women 58 years or older with varying levels of habitual physical activity levels (Table I). These subjects were part of a convenient sample set with a resting blood sample collection. The exclusion criteria for the subjects include significant cardiovascular, metabolic, or pulmonary disease, active cancer, recent treatment with anabolic steroids or corticosteroids, alcohol or drug abuse, and tobacco use. This group of subjects has varying levels of habitual physical activity, which made for a cohesive analysis of a range of habitual physical activity levels for older adults and their resting BDNF levels.

Measures

The habitual physical activity levels were measured objectively utilizing the gold standard method, accelerometers. The accelerometers (Actical, Phillips Respironics – Bend, Oregon were worn by the subjects for seven consecutive days and were only taken off during sleep and showering. Height was measured using a standard stadiometer. The subject's weight and body composition were measured via bioelectrical impedance analysis (Tanita – Arlington Heights, Illinois). The BMI was calculated with the measurements of height and weight.

The blood serum samples were collected via antecubital veins by venipuncture. The blood samples were drawn utilizing sterile procedures. The blood serum was stored at -80 degrees Celsius until it was analyzed for BDNF levels. The BDNF levels were assessed by an Enzyme-Linked Immunosorbent Assay (ELISA; RayBiotech – Peachtree Corners, GA). The CV reported by RayBiotech was <10% for intra-assay variability and <12% for inter-assay variability. The dilution factor suggested in the RayBiotech manual was between 5-500-fold. Dilution testing

was done at 1:10, 1:100, and 1:250 based off previous publication suggestions, and 1:100-fold dilution was determined as the best fit for the standard curve. CRP was quantified using a high-sensitivity, solid-phase sandwich ELISA (R&D Systems – Minneapolis, MN). All ELISA plates were read using a microplate reader (BioTek – Winooski, VT). Blood lipids were analyzed using the Cholestech LDX Analyzer (Abbott Park, IL)

Statistical analysis

Prior to data analysis, all data was tested for normality and equal variance. Pearson correlations in Statistical Package for the Social Sciences (SPSS) Version 28 (IBM Corporation – Armonk, NY) were used to assess the relationship between serum-BDNF and habitual physical activity levels, in addition to sex, BMI, total cholesterol, CRP, and BF%. A paired t-test was used to measure the differences in the data due to sex. Significance was defined as $p < 0.05$. Additionally, partial bivariate Pearson correlations were run controlling for sex.

Table 1 Participant Characteristics by sex (*n=68*)

	Total (*n=68*)	Male (*n=19*)	Female (*n=49*)
Health Measures			
Age (years)	68.4 (5.9)	68.3 (5.7)	68.5 (6.0)
BMI	26.1 (6.0)	25.9 (5.2)	26.1 (6.4)
Body *fat* (%)	31.4 (11.0)	22.9 (8.5)	34.6 (10.1)*
Total Cholesterol (mg/dL)	199.1 (35.9)	179.2 (31.5)	206.8 (34.8)
CRP (mg/dL)	1.9 (2.3)	1.6 (2.3)	2.0 (2.3)
BDNF (ng/mL)	10.4 (4.0)	7.7 (3.2)	11.4 (3.8)*
Subjective PA: CHAMPS			
MVPA (kcal/day)	2,250.3 (1,442.2)	3,149.9 (1,730.5)	1,923.2 (1,182.7)*
Objective PA: Accelerometer			
Moderate PA (min/day)	62.8 (28.3)	66.4 (28.73)	61.4 (28.3)
Light PA (min/day)	126.9 (76.3)	113.1 (40.8)	132.4 (86.4)
Counts (per min)	118.0 (55.6)	134.6 (67.0)	111.4 (49.7)

Note: Results written as Mean (SD).
*= Significant difference between men and women (*p<0.05*)

Chapter III

Results:

The average participant characteristics by sex are shown in Table 1. T-tests were run to compare all variables between men and women. There was a significant difference in serum-BDNF between men (M=7.6, SD=3.2) and women (M=11.4, SD=3.8); 3.82(66), $p<0.001$. Additionally, there was a significant difference in body fat percentage between men (M=22.9, SD=8.5) and women (M=34.6, SD=10.1); 4.48(66), $p<0.001$. Finally, there was a significant difference in moderate-vigorous PA levels between men (M=3,149.9, SD=1,730.5) and women (M=1,923.2, SD=1,182.7); -3.12(58), $p<0.001$.

Table 2 reports all correlations between serum-BDNF and health variables, not controlling for sex. Serum BDNF has a significant positive correlation with body fat percentage (*r=0.35, p=0.003*). Table 3 reports all correlations between serum-BDNF and health variables, while controlling for sex. Serum BDNF had no other significant correlations with any other anthropometric and PA variables (Table 4). The subjects had an average of 62.8 (SD =28.2) minutes per day of moderate to vigorous PA, ranging from 18.7 to 136.3 minutes per day. The subjects also reported an average of 2,250.3 (SD=1,442.2) kcals per week of energy expenditure from moderate to vigorous PA.

Table 2 Pearson Correlations between BDNF and other health variables

	Total (*n=66*)	Male (*n=19*)	Female (*n=47*)
Age (years)	-0.15	-0.07	-0.25
BMI	0.18	0.06	0.26
Total Cholesterol	0.20	0.31	0.02
BF %	0.35*	0.12	0.24
C-reactive protein	0.19	0.19	0.10

* = Significant difference between men and women (*p<0.05*)

Table 3 Pearson Correlations between BDNF and other health variables, controlling for sex

	Total (*n=66*)	Male (*n=19*)	Female (*n=47*)
Age (years)	0.06	-0.07	-0.20
BMI	0.19	0.06	0.22
Total Cholesterol	0.12	0.31	-0.02
BF %	0.18	0.11	0.21
C-reactive protein	0.03	0.19	0.16

Table 4 Pearson Correlations between BDNF and PA variables, controlling for sex

	Total	Male	Female
MVPA (kcal/week)	-0.09 (*n=68*)	-0.13 (*n=16*)	-0.07 (*n=44*)
Moderate PA (min/week)	0.14 (*n=65*)	0.14 (*n=18*)	0.15 (*n=47*)
Light PA (min/week)	-0.05 (*n=66*)	0.11 (*n=19*)	-0.08 (*n=47*)
Sedentary (min/week)	0.11 (*n=65*)	-0.24 (*n=19*)	0.18 (*n=46*)
Counts (per minute)	0.19 (*n=63*)	0.14 (*n=18*)	0.22 (*n=45*)

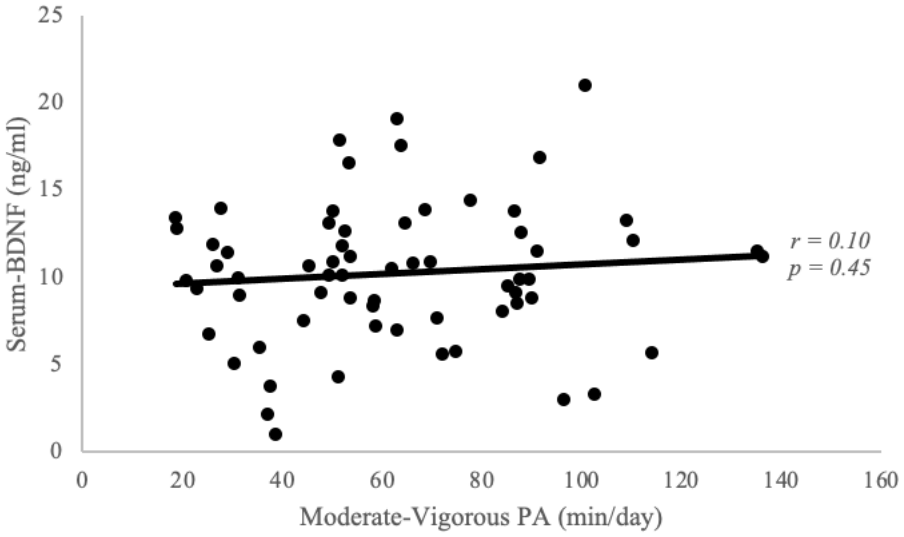

Figure 1. The relationship between serum-BDNF and objectively measured habitual moderate to vigorous PA minutes per week for all participants.

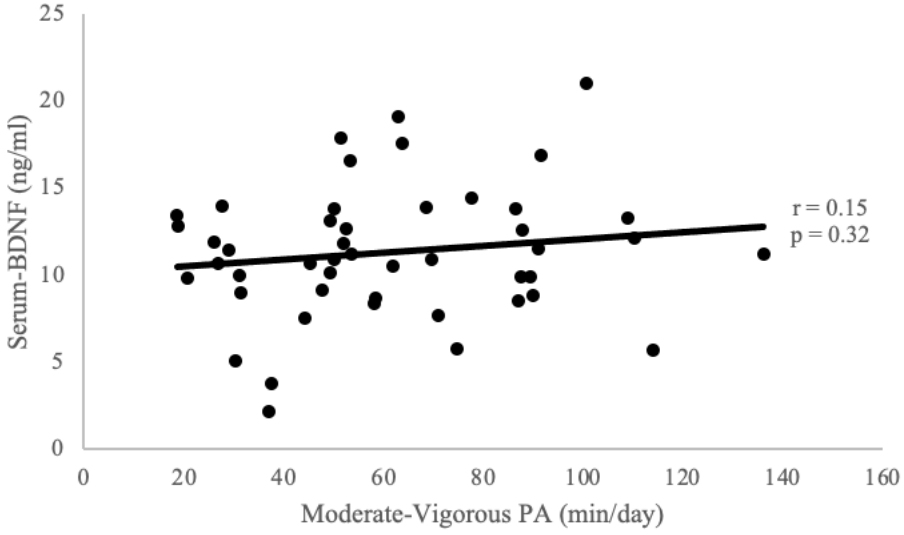

Figure 2. The relationship between serum-BDNF and objectively measured habitual moderate to vigorous PA minutes per week for female participants.

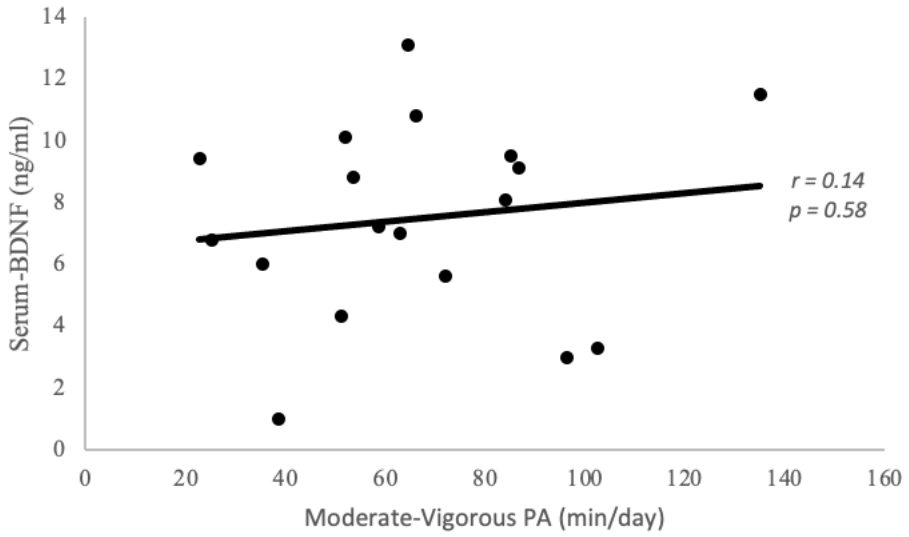

Figure 3. The relationship between serum-BDNF and objectively measured habitual moderate to vigorous PA minutes per week for male participants.

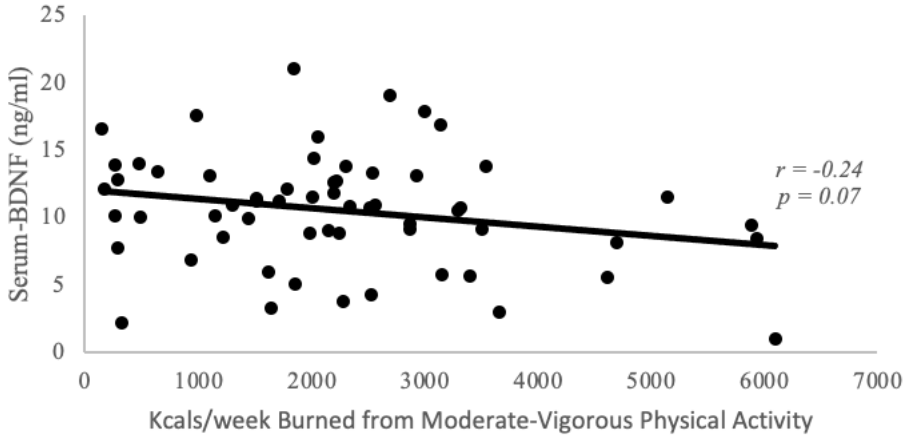

Figure 4. The relationship between serum-BDNF and subjectively measured habitual moderate to vigorous PA via Kcals/week burned for all participants.

Chapter IV

Discussion:

The purpose of this study was to examine the relationship between serum-BDNF levels and habitual PA levels in older adults. Our hypothesis was that adults with higher levels of habitual PA levels would have higher levels of resting serum-BDNF levels. This study did not support our hypothesis. We found that objectively measured PA via accelerometers, was not correlated with serum-BDNF levels. We also found that subjectively measured PA via the CHAMPS survey was not correlated with serum-BDNF levels. The secondary aim of this study was to investigate the relationship between anthropometric and serum-BDNF levels. There was a significant relationship between body fat percentage and serum-BDNF levels. However, we found that there was a significant sex difference between serum-BDNF levels and body fat percentage. Specifically, higher levels of body fat percentages are correlated with higher serum-BDNF levels (Table II).

BDNF is a neurotrophin that is involved in memory and plasticity changes in the brain. BDNF can also stimulate and control the growth of new neurons in the brain (Bathina, 2015). There is evidence that shows low levels of serum-BDNF are associated with neurological degeneration (Erikson, 2010). BDNF is actively found in the hippocampus, basal forebrain, and frontal cortex, but can also be evaluated in the blood serum samples due to the permeability of the blood-brain barrier (Bathina, 2015). Studies state that peripheral BDNF is stored in the platelets, and platelets can't cross the blood-brain barrier (Gejl, 2019). However, BDNF from the CNS can cross the blood-brain barrier through blood plasma (Gejl, 2019). BDNF in blood serum is increased by short bouts of acute exercise and is attenuated for 24-hours. Fewer studies have looked at PA effects on BDNF regulation, and how lifestyle changes can affect that regulation.

Previous studies have shown a significant increase in resting serum-BDNF levels due to exercise interventions. However, this increase in serum-BDNF levels was only in women and not men (Glud, 2019; Lommatzsch, 2006; Chan, 2017). Thus, independent t-tests and partial correlations controlling for sex were conducted in this study to evaluate sex differences and to control for the effect of sex on our associations. In the present study, our only significant correlation was between resting BDNF and body fat percentage. Counterintuitively, a higher body fat percentage was associated with higher resting BDNF levels. However, when controlling for sex, the significant correlation between body fat percentage and resting BDNF goes away.

Women have been shown to have higher resting serum-BDNF levels and tend to have higher body fat percentages than men (Karastergiou, 2012). Physiologically, women have a higher essential body fat percentage than men, at 12 and four percent respectively. Therefore, sex is a better determinant for BDNF than body fat percentage is.

Several researchers have studied the sex differences in BDNF signaling and expression and found that female subjects have higher BDNF levels in the pre-frontal cortex than male subjects (Chan, 2017; Hayley, 2015). The clinical implications of different levels of BDNF in regions of the brain can influence memory and aging diseases. Additionally, several studies have shown a significant sex difference in circulating BDNF levels due to the variation in hormones between male and female participants (Glud, 2019; Weickert, 2019; Watts, 2018; Chan, 2017). Women have higher levels of estrogen and estrogen can induce the TrkB and BDNF signaling (Wei, 2019). These hormonal effects on BDNF are also shown in Dong, et al's study, where they found BDNF regulates endometrial cells and that peripheral BDNF fluctuates in women during the phases in the menstrual cycle (2017). Our study further demonstrates the need for future analysis to be focused on the sex differences in BDNF levels and signaling.

Regardless of how physical activity was measured (via self-report or objectively using 7-day accelerometry), our results showed no significant correlations between habitual physical activity levels and resting serum-BDNF levels, which did not support our hypothesis. In agreement with our study, other researchers have also found no significant correlations between habitual PA and resting serum-BDNF levels (Beltran-Valls, 2018; Maass, 2016). Beltran-Valls, et al. utilized objective accelerometers to collect PA data. Their adolescent subjects had an average of 81.4 ± 24.3 minutes/day of moderate activity and 14.0 ± 8.1 minutes/day, which exceeds the physical activity recommendations from the ACSM. They found no significant correlation between BDNF levels and PA. Similarly, Maass, et al. saw no significant change in resting serum-BDNF in healthy adults after a 3-month exercise intervention of 30 minutes of interval training, 3 days per week. These studies suggested that the reason for this could be the increased BDNF uptake into the CNS due to increases in activity levels (Beltran-Valls, 2018; Maass, 2016). In agreement with our study, these also have high levels of physical activity among their subjects, without access to participants with lower levels of physical activity. This inadvertent recruitment of subjects that were mainly meeting physical activity recommendations

can be attributed to healthier individuals being more likely to want to participate in research studies.

There were several limitations to this study. One limitation was that a convenient sampling of subjects was used, which limited the range of habitual physical activity levels of our subjects. Our subjects had an average of 62.8 (28.3) minutes per day. Our subjects had an average of 126.8 (76.3) minutes of light physical activity per day. The averages for the group exceed the ACSM guideline of 150 minutes of moderate-intensity aerobic activity per week, making them a healthy group of individuals. Although we had a wide range of activity levels, the average activity level of the group was high, exceeding the daily activity recommendation. We only had four individuals fall below the weekly recommendation for moderate-intensity exercise, which could have influenced the lack of significance seen in our results. This gave us only a portion of the population to analyze, which made it difficult to see the full picture without the lower levels of PA. A second limitation was the small sample size due to the convenient sampling. Although the subject size was larger than in previous studies, it was still smaller than we would have liked. A third limitation of the study was only having access to samples at rest. Future studies should analyze effects of an exercise intervention on resting BDNF serum levels and BDNF serum levels after an acute bout of exercise, after a training intervention.

In conclusion, this study further strengthens our knowledge that there are true sex differences in serum-BDNF between men and women. Our hypothesis was not supported, and we found no relationship between serum-BDNF levels and habitual physical activity levels (objectively and subjectively measured). This aligns with previous research; however additional studies should be conducted to better understand the sex differences in serum-BDNF between men and women. Future research should focus on those sex differences and its clinical implications for those with dementia and AD.

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