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Physical Exercise and Serum BDNF Levels: Accounting for the Val66Met Polymorphism in Older Adults

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Background: Brain-derived neurotrophic factor (BDNF) expression, which can be measured in blood serum, has been found to increase with aerobic exercise. The link between BDNF level, physical exercise, and genetic status (Val66Met polymorphism) has not been well researched in older adults.

Objective: To investigate the possible link between BDNF expression, acute aerobic exercise, and the Val66Met polymorphism in older adults.

Method: Twenty-three healthy older adults participated in one session of acute aerobic exercise. Their serum BDNF levels were measured both at baseline and post exercise. Saliva samples were collected to identify each individual’s genetic status.

Results: At baseline, the individuals’ mean serum BDNF level was 16.03 ng/mL (Val66Val = 15.89 ng/mL; Val66Met = 16.34 ng/mL); post exercise, the individuals’ mean serum BDNF level was 16.81 ng/mL (Val66Val = 16.14 ng/mL; Val66Met = 18.34 ng/mL).

Conclusion: One session of acute aerobic exercise significantly increased the individuals’ mean serum BDNF level. Males had higher BDNF levels than females. There was a significant interaction between gender and BDNF expression post exercise and a significant between-group effect of gender. The Val66Met carriers had a more positive response to the acute aerobic exercise compared with the Val66Val carriers, although without a significant difference between the two groups.

Key Words: brain-derived neurotrophic factor, BDNF, physical exercise, Val66Met polymorphism, aging

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BDNF = brain-derived neurotrophic factor. BMI = body mass index. HR = heart rate.

The connection between physical exercise and improved brain health has been established repeatedly (Alomari et al, 2013; Hötting et al, 2016; Ratey and Loehr, 2011). Physical exercise is thought to modulate cognition by reducing stress and inflammation, improving insulin sensitivity, and increasing blood flow to several neural structures (Kennedy et al, 2017). Specifically, aerobic exercise has been found to increase hippocampal expression of the brain-derived neurotrophic factor (BDNF) protein, which is related to improved cognition and memory (Håkansson et al, 2017; Kramer et al, 2006; Saucedo Marquez et al, 2015).

BDNF and Aerobic Exercise

BDNF is a small protein that belongs to a class called neurotrophic factors. These factors are known to exert neuroplastic effects across several neural structures such as the hippocampus, hypothalamus, and cerebellum, as well as throughout the cerebral cortex (Lista and Sorrentino, 2010; Montag et al, 2014). Aerobic exercise describes the type of physical exercise that relies on the metabolic conversion of oxygen from the blood to the muscles. It is this metabolic conversion that enables us to engage in physical activity over time (Griffin et al, 2011).

Binding to a specific cell surface receptor called tropomyosin receptor kinase B, BDNF can trigger excitatory or inhibitory signaling cascades, resulting in neural survival, growth, and differentiation (Erickson et al, 2012). Several researchers have posited that the cognitive benefits reaped by physical exercise may not originate exclusively from the increased perfusion of blood to the brain, but also from additional BDNF expression in the hippocampal structure (Alomari et al, 2013; Maass et al, 2016; Ratey and Loehr, 2011).
**BDNF and Genetics**

The most common genetic modifier of the BDNF is a single nucleotide polymorphism known as Val66Met or rs6265. This polymorphism leads to an amino acid substitution of valine to methionine at codon 66 (Egan et al., 2003). Animal studies have shown that the substitution of one or two Val alleles with a Met allele leads to decreased exercise-dependend BDNF expression in the hippocampus, which in turn negatively affects hippocampal plasticity and memory formation (Ieraci et al., 2016).

Although these results have yet to be explicitly confirmed in humans, measuring hippocampal memory functions in Val and Met carriers has led to an assumption that these effects are also present in humans (Hopkins et al., 2012). Researchers have also found that aging can magnify the effects of this polymorphism (Li et al., 2010), and that the presence of at least one Met allele can account for individual differences in age-related hippocampal dysfunction (Erickson et al., 2012).

Some of the previous genome-wide association studies have found that BDNF levels are related to the Val66Met polymorphism; however, not all of the studies have confirmed this finding (Li et al., 2020; Terracciano et al., 2013). BDNF levels appear to be associated with networks that include genes that are implicated in brain aging and Alzheimer disease (Li et al., 2020).

**Serum BDNF Levels**

The BDNF can cross the blood–brain barrier (Saucedo Marquez et al., 2015). Studies have found a high blood–brain barrier correlation when comparing hippocampal BDNF expression with BDNF levels that were found in the blood of rodents and pigs. Hence, BDNF expression in the brain can be assessed by analyzing either blood plasma or serum (Radka et al., 1996).

A literary review by Knaepen et al. (2010) found that studies on humans have established that one single aerobic exercise session can lead to an increase in serum BDNF levels. The effect is transient and is reliably detectable only if the blood sample is collected within 10 minutes after the exercise session. The great variation in BDNF levels across studies (from 11.7% to 410%) can, at least in part, be attributed to the difference between the exercise protocols that were used in the different studies because more intensive bouts of exercise are assumed to elicit greater BDNF responses. Other factors that may affect an individual’s BDNF expression are age (Erickson et al., 2011), gender (Dinoff et al., 2017), body mass index (BMI) (Wang et al., 2022), physical fitness level (Chan et al., 2008; Nofuji et al., 2008), and adverse life experiences (Elzinga et al., 2011).

**BDNF and Aging**

Although the correlation between serum BDNF levels, hippocampal BDNF expression, and hippocampal plasticity has not been fully established, this potential correlation carries interesting implications for older populations. Hippocampal formation is vulnerable to age-related atrophy (Miranda et al., 2019) and has an estimated structural decline of 1–2% per year in older adults (Erickson et al., 2011). Increasing hippocampal BDNF expression through aerobic exercise could be a cost-effective way to counteract this age-related hippocampal deterioration.

Only a few studies have investigated the relationship between physical exercise and BDNF levels in older adults. Some studies reported that serum BDNF levels are negatively correlated with age (Lommatzsch et al., 2005; Shimada et al., 2014; Ziegenhorn et al., 2007); others found no such correlation (Bus et al., 2012; Minelli et al., 2011).

Even fewer studies have investigated how aerobic exercise can affect BDNF levels in older adults; those that did (Håkansson et al., 2017; Måderová et al., 2019) found that serum BDNF levels temporarily increased after just one session of aerobic exercise. Måderová et al. (2019) reported that one aerobic exercise session resulted in an increase from 19.2 ± 5.1 ng/mL at baseline to 22.2 ± 6.5 ng/mL post exercise. Håkansson et al. (2017) reported a similar increase in serum BDNF levels, increasing from 19.2 ± 1.17 ng/mL at baseline to 22.5 ± 0.99 ng/mL post exercise.

Both studies (Håkansson et al., 2017; Måderová et al., 2019) found great individual variations in BDNF levels both at baseline and post exercise. These differences in BDNF level and response to the exercise session may be attributed to the presence of one or two Met alleles (Hopkins et al., 2012; Ieraci et al., 2016; Notaras et al., 2015), although genetic status was not accounted for in either study. To the best of our knowledge, the potential impact of the Val66Met polymorphism on exercise-dependent serum BDNF levels in a healthy, older, human population has not previously been investigated.

**Current Study**

We wanted to investigate the possible link between BDNF level, acute aerobic exercise, and the Val66Met polymorphism in older adults. To add to the existing literature on BDNF levels in older adults, we investigated serum BDNF levels at baseline and post one single session of aerobic exercise in healthy, older adults while accounting for their genetic status. We expected Met-carrying participants to have an attenuated response to the aerobic exercise intervention.

**METHOD**

We conducted the current study in connection with the ongoing Physical Exercise Augmented Cognitive Behavior Therapy for Older Adults With Generalized Anxiety Disorder trial. Our sample consisted of a group of healthy older adults who were to be matched against baseline data in an ongoing clinical trial (Stavestrand et al., 2019).

**Participants**

We placed an advertisement in the local newspaper inviting healthy, older adults between 60 and 75 years of age to participate in a research study on age and mental and physical health. No reward for participation was provided. The main exclusion criterion for the group was...
ongoing mental illness, substance use disorder, or substance/medication-induced disorders as determined by a Norwegian translation of the Mini International Neuropsychiatric Interview (Sheehan et al, 1998).

Additional exclusion criteria were (a) use of benzodiazepines or antipsychotic medication, (b) medical conditions that preclude participation in physical exercise, (c) lifetime history of psychosis and/or mania, (d) participation in ongoing psychotherapy, (e) organic brain disease, (f) a score of ≤25 on a Norwegian translation of the Mini-Mental State Examination (Folstein et al, 1975), and (g) currently performing physical activity throughout a typical week so that we could evaluate whether they met the study criteria. In order to ensure sufficient intensity levels and included the Mini International Neuropsychiatric Interview and the Mini-Mental Status Examination, which were both administered by a licensed psychologist (S.H.S.). A Norwegian translation of the Physical Activity Readiness Questionnaire (Cardinal et al, 1996) was used to assure that it was medically safe for each participant to complete the exercise intervention.

Next, we asked the individuals to describe their physical activity throughout a typical week so that we could evaluate whether they met the study criteria. In addition, we contacted each of the individuals’ general practitioner to ensure that it was safe for every individual to complete the exercise intervention.

Assessments

We required every participant to attend 1 full day of testing at the Solli District Psychiatric Centre in Nesttun, Norway for the collection of biological material as well as completion of the exercise intervention. This testing was carried out in the following order:
- measurement of height and weight,
- measurement of systolic and diastolic blood pressure,
- collection of saliva sample for genetic profiling of the Val66Met polymorphism,
- collection of resting blood sample for the BDNF level assessment,
- Ekblom-Bak Submaximal Cycle Stationary Bike Test (Björkman et al, 2016),
- 20 minutes of cycling,
- collection of postexercise blood sample for the BDNF level assessment, and
- measurement of aerobic capacity (VO2max) (Björkman et al, 2016).

Exercise Intervention

The exercise intervention consisted of the 8-minute Ekblom-Bak Submaximal Cycle Stationary Bike Test using a Monark stationary bike followed by 20 minutes of cycling, thereby resulting in a total of 28 minutes of aerobic exercise. The Ekblom-Bak Test consists of 4 minutes of cycling with an initial standardized light intensity level of 60 rpm with a resistance of 30W, followed by 4 minutes of individually targeted cycling with moderate intensity following standardized levels of resistance until participants reach a level between 12 and 15 on Borg’s rating of perceived exertion (60 rpm) (Björkman et al, 2016; Borg, 1970). The following 20 minutes of cycling had no criteria regarding load or step frequency but did require that each individual’s heart rate (HR) aim for ≥65% of the estimated maximum HR (Stavestrand et al, 2019), which was calculated using the formula: HRmax = 208 – (0.7 × age) (Tanaka et al, 2001).

The exercise intervention was completed under the guidance and supervision of a licensed physiotherapist (T.B.E.) or an occupational therapist. In addition to being part of the exercise intervention that was expected to increase serum BDNF levels, the Ekblom-Bak Test was also used to estimate the individuals’ maximum oxygen uptake (VO2max). Throughout the exercise intervention, T.B.E. or the occupational therapist used an HR monitor to register each individual’s HR each minute in a standardized form in order to ensure sufficient intensity levels.

Blood and Saliva Sample Collection, Storage, and Analysis

We scheduled the collection of the blood samples and the exercise intervention between 09:00 AM and 11:00 AM to ensure that potential circadian fluctuations would not impact the serum BDNF samples. Each test day started with a verbal walk-through of what testing would entail. The baseline serum BDNF sample was collected between 09:13 and 10:02 AM; the postexercise serum BDNF sample was collected within 10 minutes of completion of the exercise intervention, between 10:07 and 10:57 AM.

Both the resting (baseline) and postexercise blood samples were collected using a singular venipuncture and separation tubes. The sample tube was set aside for clotting at room temperature for 60 minutes. The sample was then centrifuged at 3000×g for 10 minutes at room temperature. The serum was transferred into 1.5-mL microtubes and frozen at −30°C. The sample was then placed in long-term storage at −70°C until analysis.

A licensed bioengineer at the University of Bergen’s Department for Biological and Medical Psychology used the enzyme-linked immunosorbent assay Human mBDNF DuoSet to analyze the serum BDNF levels. The sensitivity for this kit is 0.1 ng/mL. The BDNF analyses were run in duplicates, and the results were averaged. The interassay variation was 19.9–21.0 CV%.

The saliva samples were collected using self-collection sampling tubes and were frozen at −30°C until analysis. For genetic profiling of the BDNF gene, DNA was extracted from the saliva samples and was analyzed using the TaqMan
method (Shen et al, 2009) at the facilities of the Trøndelag Health Study at the Norwegian University of Science and Technology, Trondheim, Norway by Trøndelag Health Study personnel.

Statistical Analysis

We used SPSS software version 25 to conduct all of the statistical analyses. We used a repeated-measures ANOVA to investigate both the effects of the exercise intervention on the individuals’ serum BDNF levels and the impact of genetic status. Based on previous research, we also assessed the potential influence of the effect of age, gender, and BMI by including these variables separately as covariates in the model (Dinoff et al, 2017; Erickson et al, 2011; Wang et al, 2022).

We used Cohen’s d to determine the impact of our results by estimating the effect size for the between-group comparisons ($d = [M1 - M2]/SD$ pooled) and the within-group comparisons ($d = [M2c - M2e] - [M1e - M1c]/SD$ pooled) (Cohen, 1992). A value from 0.2 to 0.4 is considered to be a small effect size, values around 0.5 are considered to be a medium effect size, and a value $\geq 0.8$ is considered to be a large effect size.

Figures 1–3 were created using the ggrain package (Judd et al, 2023) and the ggplot package (Wickham, 2016) from RStudio Software (RStudio team, 2020).

Power Analysis

Power was determined using G*Power version 3.1.9.7. (Faul et al, 2007). Based on the study by Håkansson and colleagues (2017), which was conducted with an equivalent sample and design, an effect size of $d = 0.75$ was expected. Power was estimated for a repeated-measures ANOVA, within-between interaction with an alpha of 0.05, two groups, and two measurements. Based on the expected effect size, a power $>0.80$ would be achieved with a sample size of 20 individuals.

RESULTS

Participants

We assessed 91 individuals for participation in our study. Of those, 28 fulfilled one or several of the exclusion criteria and were not included for participation, and one individual withdrew from the study. Of the 62 participants who were eligible for inclusion, 26 completed participation before the project had to temporarily shut down due to COVID. Three individuals were excluded from the data analysis because the time lapse between the postexercise intervention and the postexercise blood sample exceeded 10 minutes. Thus, 23 individuals ($M_{age} = 69.35$ years, SD = 4.06) were included in our analyses. There were 17 females (74%). The mean serum BDNF level was 16.03 ng/mL (SD = 4.08) at baseline and 16.81 ng/mL (SD = 4.77) post exercise. Sixteen individuals (70%) were Val homozygous. Further descriptive demographic variables are shown in Table 1.

Effect of Acute Aerobic Exercise on Serum BDNF Levels

One session of acute aerobic exercise had a significant positive effect on the individuals’ serum BDNF levels, $F = 6.04, P = 0.023, d = 0.20$. Figure 1 provides a visual representation of the individual and mean serum BDNF levels at baseline and post exercise. The mean response to aerobic exercise was a 4.9% increase in serum BDNF levels post exercise.

Impact of Val66Met Polymorphism on Serum BDNF Levels in Response to Acute Aerobic Exercise

We did not find any significant interaction effect between the exercise intervention and the individuals’ genetic status, $F_{1, 21} = 3.65, P = 0.070$. Postexercise, the mean difference between the Val66Val carriers and the Val66Met carriers yielded a Cohen’s $d$ of 0.43. When looking at serum BDNF levels pre and post exercise, effect size analysis within the Val carriers at the two different points in time yielded a Cohen’s $d$ of 0.06, and effect size analysis within the Met carriers yielded a Cohen’s $d$ of 0.36. Figure 2 provides a visual representation of the individual and mean serum BDNF levels at baseline and post exercise, sorted by genetic status.

The Val carriers exhibited a mean increase of 1.6% in serum BDNF levels post exercise (baseline: $M = 15.89$, SD = 3.64; post exercise: $M = 16.14$, SD = 4.22). The Met carriers exhibited a mean increase of 11.6% post exercise (baseline: $M = 16.34$, SD = 5.27; post exercise: $M = 18.34$, SD = 5.92).

Relationship With Age, Gender, and BMI

To assess the influence that age, gender, and BMI had on the effects of the exercise intervention, we entered the three variables into the model separately. A significant interaction between gender and change in BDNF levels post exercise was found, $F_{1, 20} = 9.77, P = 0.025$, but there was no significant interaction in the equivalent analyses for age or BMI, $F_{1, 20} = 0.28, P = 0.602$, $F_{1, 20} = 1.13, P = 0.300$, respectively. There also was a significant between-subjects effect of gender, $F_{1, 20} = 6.65, P = 0.018$, indicating a significant effect of gender across time. Including gender in the model also increased the $P$ value for the interaction between the exercise intervention and genetic status, $F_{1, 20} = 4.12, P = 0.056$, underlining the impact of gender on this relationship. Figure 3 provides a visual representation of the individual and mean serum BDNF levels at baseline and post exercise, sorted by gender.

DISCUSSION

BDNF and Aerobic Exercise

The current study is the first to investigate BDNF expression following one single session of acute, aerobic exercise in healthy, older adults while accounting for the Val66Met polymorphism. The results support previous findings that acute, aerobic exercise leads to an increase in serum BDNF levels in older adults. On average, the
individuals in our study exhibited a significant rise in serum BDNF levels of 4.9% post exercise, with a small effect size. We also found a significant effect of gender on serum BDNF levels, as well as an interaction between the two time points. Though nonsignificant, the results also indicate that Met carriers may experience a more pronounced response to aerobic exercise than their Val-carrying counterparts.

Although significant, the overall increases in serum BDNF levels were lower than the values that were detected in two previous studies (Håkansson et al, 2017; Máderová et al, 2019). The difference between exercise interventions could help explain these discrepancies. Håkansson and colleagues (2017) had their participants engage in a full-body aerobic workout, and Máderová and colleagues (2019) had their participants engage in a 40-minute cycling program. Both of these exercise interventions were more intensive than the one we used and may explain why they elicited a higher serum BDNF response.

One additional difference between our study and that of Máderová and colleagues (2019) is that the mean BMI of their participants was higher (MBMI = 27.1, SD = 3.2) than the mean BMI of our participants (MBMI = 24.4, SD = 2.7). BMI was not a significant covariate in our study. A recent meta-analysis of physical exercise and BDNF levels found that BNDF levels increased significantly only in individuals with a baseline BMI of ≥25 (Wang et al, 2022), which is higher than the mean BMI in our study.

**BDNF and Gender**

In line with previous studies (Knaepen et al, 2010), the postexercise BDNF levels of the individuals in our study demonstrated great individual variation (Figure 1). Males had significantly higher levels of serum BDNF than females, both at baseline and post exercise. Furthermore, we found a significant interaction between gender and an increase in serum BDNF levels post exercise. These findings are in accordance with the meta-analysis by Dinoff et al (2017), which reported larger increases in BDNF levels post exercise in studies with a greater proportion of male participants. Our sample contained 74% females; Håkansson and colleagues' (2017) sample contained 57.9% females. As such, the large proportion of females in our study might partially explain the lower observed total changes in BDNF levels post exercise in our study, as well as the lower effect size.

**BDNF and Genetics**

Although the difference between the Val carriers and their Met-carrying counterparts was nonsignificant, the Met
carriers exhibited a more positive response (M = 11.6%) to the exercise session compared with the Val carriers (M = 1.6%). Because previous literature has pointed to Met carriers exhibiting attenuated BDNF responses to physical exercise (Hopkins et al, 2012; Ieraci et al, 2016), this finding was surprising. Although the aforementioned studies were conducted either on animals or on younger adults, they did lead to an overall assumption that Met carriers generally have attenuated BDNF responses to exercise. If the results of our study are any indication of a larger pattern, our results could indicate that Met carriers become more susceptible to exercise-dependent BDNF levels as they age. This finding would also raise the question of whether BDNF-dependent plasticity in the hippocampus could be affected by this change in serum BDNF response between Val carriers and Met carriers. This implication would be most relevant to an aging population, as previous findings have indeed pointed toward a change in the action or impact on cognition of these genetic variants with age (Erickson et al, 2008).

Because the impact of the Met polymorphism on exercise-dependent serum BDNF levels in healthy, older, human populations has not previously been investigated, it is important to acknowledge that of the 23 individuals who were included in our study, only seven were Met carriers. More than anything, our findings underline how little is known about the interaction between the Val66Met polymorphism and exercise-dependent BDNF levels in this age group. Other variables such as the intensity of the exercise session, overall physical fitness (Chan et al, 2008; Nofuji et al, 2008), early adverse life experiences (Elzinga et al, 2011), and age (Erickson et al, 2011) could influence individual BDNF responses in a sample of this size. Future research should therefore focus on investigating these effects in larger samples of older adults in order to ensure that different variables can be accounted for. It is also important that similar exercise interventions and extensive demographic data collection are standardized across studies.

**Study Strengths and Limitations**

The current study used a detailed participant screening process with a strong set of exclusion criteria. These criteria should count as a strength because the
FIGURE 3. Individual and mean serum BDNF levels at baseline and post exercise in males and females, measured in nanograms per milliliter (ng/mL). The mean values are highlighted as tinted dots and line. BDNF = brain-derived neurotrophic factor.

TABLE 1. Descriptive Statistics for Continuous Variables

<table>
<thead>
<tr>
<th>Variable</th>
<th>n†</th>
<th>Min.</th>
<th>Max.</th>
<th>M</th>
<th>SD</th>
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</thead>
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<tr>
<td>Age (years)</td>
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<td>75.00</td>
<td>69.35</td>
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<td>Systolic blood pressure (mm Hg)</td>
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<td>177.00</td>
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<td>17.57</td>
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<td>98.00</td>
<td>81.75</td>
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<td>Body mass index (cm/kg)</td>
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<td>2.89</td>
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<td>Mini-Mental State Examination score</td>
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<td>30</td>
<td>29.61</td>
<td>0.58</td>
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<td>3.42</td>
<td>2.89</td>
<td>0.39</td>
</tr>
<tr>
<td>VO2_max (L/min) females</td>
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<td>1.51</td>
<td>2.37</td>
<td>1.89</td>
<td>0.29</td>
</tr>
<tr>
<td>VO2_max (mL/kg/min) males</td>
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<td>43</td>
<td>34.55</td>
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<tr>
<td>VO2_max (mL/kg/min) females</td>
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<td>5.35</td>
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<td>64</td>
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<tr>
<td>Average HR after Ekblom-Bak min 7–8</td>
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<td>114.29</td>
<td>11.99</td>
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<td>Total serum BDNF ng/mL baseline</td>
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<td>8.90</td>
<td>23.50</td>
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<tr>
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<td>9.70</td>
<td>27.70</td>
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<td>8.90</td>
<td>22.50</td>
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<td>3.64</td>
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<tr>
<td>Val66Val serum BDNF ng/mL post exercise</td>
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<td>4.22</td>
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<td>12.20</td>
<td>27.70</td>
<td>18.34</td>
<td>5.92</td>
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</table>

†n values vary because of reporting errors.

BDNF = brain-derived neurotrophic factor. HR = heart rate. VO2_max = maximum oxygen uptake.
measures ensured a relatively homogenous selection of participants. The fact that the individuals who were analyzed in this study were a part of a larger study also ensured that strict protocols entailing both physical and biological testing were carried out by professionals, thereby ensuring further homogeneity across testing and data collection within the sample. Additionally, ours is one of very few studies that have investigated the effects of acute aerobic exercise on serum BDNF levels in older adults, and as far as we are concerned, the only study to also account for the Val66Met polymorphism.

A limitation of the current study is the small sample size (N = 23), with only seven Met carriers included. It is important to note, though, that both Máderová and colleagues (2019) and Håkansson and colleagues (2017) had similarly small sample sizes of 22 and 19 participants, respectively. Therefore, the sample size of our study is not uncommonly small compared with existing research on the topic. Although our power analysis indicated that the sample size was sufficient to detect a statistically significant interaction effect, a larger sample size is required to detect a significant effect, given the observed effect sizes in our sample. The expected and unequal distribution of observed alleles also affects the power to detect significant effects. As such, future studies on larger sample sizes are warranted.

CONCLUSION

The aim of our study was to investigate the possible link between BDNF expression, acute aerobic exercise, and the Val66Met polymorphism in older adults. One session of acute aerobic exercise significantly increased mean serum BDNF levels for all of the participants combined. Males had a significantly higher level of BDNF than females did, and there was a significant interaction between gender and change in BDNF levels after a single session of aerobic exercise. Although nonsignificant, the pattern detected in this study implies that Val66Met carriers may have a more positive response to acute aerobic exercise compared with Val66Val carriers.

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