Author/s:
Ashcroft, SK;Basclain, K;Woolnough, C;Hoon, MW;Walsh, SJ;Starc, LC;Johnson, L;Kuys, SS;Thompson-Butel, AG

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Concomitant Increases in Brain-Derived Neurotrophic Factor and Lactate Post-Exercise Do Not Demonstrate a Direct Correlation

S. K. Ashcroft[1] | K. Basclain[1] | C. Woolnough[2] | M. W. Hoon[1] | S. J. Walsh[1] | L. C. Starc[1] | L. Johnson[3,4] | S. S. Kuys[5] | A. G. Thompson-Butel[1]

[1]School of Behavioural and Health Sciences, Australian Catholic University, Strathfield, New South Wales, Australia | [2]Department of Chemical Pathology, Royal Prince Alfred Hospital, Camperdown, New South Wales, Australia | [3]School of Behavioural and Health Sciences, Australian Catholic University, Fitzroy, Victoria, Australia | [4]Melbourne School of Health Sciences, Physiotherapy Department, University of Melbourne, Parkville, Victoria, Australia | [5]School of Allied Health, Australian Catholic University, Queensland, Australia

Correspondence: A. G. Thompson-Butel (angelica.thompsonbutel@acu.edu.au)

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ABSTRACT

The aim of this study was to determine the relationship between BDNF and lactate concentration, accounting for genotype and sex, before and after a submaximal graded exercise test in 31 adults (37.5 ± 14.0 years, 54.8% female). The presence of the Val66Met polymorphism was identified at baseline, and BDNF and lactate concentrations were measured before and after exercise. Pearson's correlation coefficient was used to determine the relationship between BDNF and lactate concentration at pre- and post-exercise, and change in concentration (post- minus pre-exercise). The Val66Met polymorphism was identified in 11 participants (35%, seven females). An increase in BDNF and lactate concentration was observed from pre- to post-exercise ($p < 0.001$), but no significant correlation between the two measures was observed at pre-exercise ($r = -0.256$, $p = 0.164$), post-exercise ($r = 0.112$, $p = 0.549$), and change in concentration ($r = 0.019$, $p = 0.921$). A moderate inverse correlation was observed in participants with the Val66Met polymorphism ($r = -0.744$, $p = 0.009$) and males ($r = -0.695$, $p = 0.006$) at pre-exercise. The results show that while BDNF and lactate concentrations increased following a submaximal graded exercise test, there is little evidence to suggest a relationship exists between BDNF and lactate.

1 | Introduction

Brain-Derived Neurotrophic Factor (BDNF) is a neurotrophin essential for brain development and neuronal survival within the central and peripheral nervous systems (Molinari et al. 2020). BDNF is a biomarker of neuroplasticity (Balkaya and Cho 2019; Bang 2017), associated with neurogenesis and neuroprotection (Wlodarczyk et al. 2021), and brain repair following injury (Liu et al. 2020). BDNF is secreted in an activity-dependent manner (Knaepen et al. 2010) from both neurons and axons in response to neuronal activity, and binds to tropomyosin-related kinase receptors (Balkaya and Cho 2019). Through its affinity with tropomyosin receptor kinase B (Ibrahim et al. 2022), BDNF can influence neuro-morphological development and synaptic activity (Cassidy and Cramer 2017). Exercise is proposed to increase BDNF transcription within the brain, with increased secretion from cerebral vascular endothelium (Rasmussen et al. 2009). It is also proposed that BDNF is produced within the skeletal muscle bed in response to muscle contraction during exercise (Matthews et al. 2009). Higher levels of basal BDNF are associated with enhanced

Summary

- Measuring the effect of exercise on neuroplasticity may be useful to determine the effects of interventions on age-related cognitive decline and recovery following neurological injury.
- To the best of the researchers' knowledge, this is the first study to examine the relationship between BDNF and lactate while accounting for the presence of biological sex and the Val66Met polymorphism, which are proven confounders of BDNF concentration in adult populations.
- This preliminary study demonstrates that lactate cannot be used interchangeably with BDNF in most subgroups; however, increased lactate concentration may indicate an increased BDNF concentration.

cognitive processes such as memory formation and recall (van Dongen et al. 2016; Zenke et al. 2015). However, age-related declines in BDNF concentration are also evident (Walsh et al. 2020).

Lactate is a metabolic by-product (Rabinowitz and Enerbäck 2020) of muscle glycolytic pathways during exercise (Skriver et al. 2014), with increases in blood lactate concentration observed following an acute bout of high-intensity aerobic exercise (Tsukamoto et al. 2016b). Like BDNF, lactate is a signaling molecule associated with various neurological processes, including synaptic plasticity and brain excitability (Herrera-López and Galván 2018), memory and learning (Hu et al. 2021; Margineanu et al. 2018). Capillary blood lactate is also commonly used within healthy populations as a measure of exercise intensity (Hu et al. 2021; Schiffer et al. 2011; Tsukamoto et al. 2016a). Lactate is linked with BDNF concentration in healthy individuals (Hu et al. 2021; Coco et al. 2013), with metabolic lactate crossing the blood–brain barrier and inducing BDNF expression within the hippocampus, facilitating lactate-dependent BDNF increases (El Hayek et al. 2019). This lactate-dependent increase in BDNF concentration is also associated with improved memory formation (El Hayek et al. 2019). However, the interaction between BDNF and lactate is not well understood (Mueller et al. 2020). Potential mechanisms that have linked both BDNF and lactate include NMDA-receptor activation or silent information regulator 1 (SIRT1) activation of the peroxisome proliferator-activated receptor γ co-activator α (PGC1α)/fibronectin type III domain-containing 5 (FNDC5)/BDNF pathway via silent information regulator 1 (SIRT1) activation (El Hayek et al. 2019; Mueller et al. 2020). Following high intensity aerobic exercise, elevated blood lactate concentrations are associated with increased BDNF gene expression through the release of glutamate and BDNF at the presynaptic terminals (Torabi and Ahmadi 2024). This subsequently enhances the glutamate-NMDA pathway (Torabi and Ahmadi 2024; Lou et al. 2008). However, an inverse U-shaped dose–response between exercise intensity and BDNF gene expression may exist, which may be attributed to the large quantities of lactate produced during high intensity aerobic exercise (Torabi and Ahmadi 2024).

The benefits of aerobic exercise are robust and wide ranging, including improvements in cardiorespiratory fitness, anthropometric measures, and cardiovascular disease risk factors (Martland et al. 2020). High intensity aerobic exercise (≥76% heart rate maximum (Bayles et al. 2023)) can produce large and statistically significant increases in BDNF concentration in healthy adult cohorts (Antunes et al. 2020; Rojas Vega et al. 2006; Saucedo Marquez et al. 2015). High intensity aerobic exercise is also demonstrated to stimulate the endocrine system, resulting in increased concentrations of cortisol and testosterone, two markers of training stress (Sayyah et al. 2019). Physiological responses associated with high intensity aerobic exercise such as increased blood lactate concentration may also facilitate improved executive function (Ai et al. 2021) and memory (Kovacevic et al. 2020) in adults. Therefore, utilizing high intensity aerobic exercise in clinical practice to improve health may facilitate increases in BDNF concentration and subsequent improvements in cognitive processing, mitigating age-related BDNF decline.

The measurement of biomarkers of neuroplasticity may be beneficial in exercise prescription and in clinical rehabilitation settings to allow the personalization of exercise to produce neuroplastic benefits. BDNF testing is an invasive procedure that involves the collection and analysis of blood that typically requires specialized phlebotomy and biochemistry training, and expensive equipment (Gonzalez et al. 2018). While there is the option for BDNF analysis to be outsourced to testing facilities, this is often an expensive and a logistical challenge to organize transportation and analysis (Gonzalez et al. 2018). In addition, the collection and analysis of samples to quantify BDNF concentration is not within the scope of allied health professionals that are tasked with providing interventions that target neuroplasticity or age-related cognitive decline (Australian Physiotherapy Association 2011; Exercise and Sports Science Australia 2015). Therefore, there is limited capacity to monitor the effectiveness of exercise interventions on neuroplasticity in clinical practice settings due to the impracticality of current BDNF testing and analysis procedures.

Like BDNF, lactate is an important substrate associated with brain plasticity (Coco et al. 2013) and memory formation (Hu et al. 2021; Margineanu et al. 2018). The measurement of lactate concentration is also easier than BDNF concentration in clinical practice, requiring a smaller blood sample, and is within the scope of practice of health professionals delivering exercise interventions (Bayles et al. 2023; Crotty et al. 2021). While lactate concentration is commonly used as a measure of aerobic exercise intensity (Skriver et al. 2014; Tsukamoto et al. 2016b; Tsukamoto et al. 2016a), a correlation may exist between BDNF and lactate concentration (Antunes et al. 2020; Rojas Vega et al. 2006; Ferris et al. 2007; García-Suárez et al. 2020). Previous literature has explored the effect of a ramp incremental exercise test on BDNF and lactate concentrations in a small sample of male athletes only, but no significant correlation was identified between the variables (Rojas Vega et al. 2006). An inverse correlation was identified between lactate and BDNF following an acute high intensity aerobic exercise session in young adult males (Antunes et al. 2020), while a positive correlation was identified following a graded exercise test in a mixed adult cohort (26% female) (Ferris et al. 2007). The use of biofeedback is suggested to allow for individualized physiological training practices to be developed, which may allow training parameters to target the individual's needs for improved athletic performance (Navabinejad and Mind 2023). In clinical practice, the use of a more clinically feasible measurement of neuroplasticity biomarkers is recommended to facilitate greater personalization

of exercise prescriptions and rehabilitation programs, in particular for individuals with stroke (Bernhardt et al. 2016) or cognitive decline (Weinstein et al. 2014) where exercise to increase BDNF is recommended for better prognosis.

The Val66Met polymorphism is the most common BDNF genetic variation, occurring because of the substitution of a valine (Val) with a methionine (Met) allele at codon 66 of the BDNF gene (Balkaya and Cho 2019). The Val66Met polymorphism is present in 20%–30% of the Caucasian population and up to 70% within the Asian population (Knaepen et al. 2010). However, existing studies exploring the relationship between BDNF and lactate before and after exercise did not account for the presence of the Val66Met polymorphism (Antunes et al. 2020; Ferris et al. 2007). The presence of the Val66Met polymorphism is associated with reduced BDNF secretion (Egan et al. 2003; Hariri et al. 2003) and a diminished response to exercise in healthy adult males (Lemos et al. 2016). BDNF concentration may also be confounded by biological sex (Chan and Ye 2017). It is proposed that differences exist in the expression, function, and signaling of BDNF, which may be attributed to the variation in body weight and composition, as well as hormonal differences between males and females (Chan and Ye 2017). However, no study has explored the effect of biological sex on the correlation between lactate and BDNF concentration in a mixed sex healthy adult cohort.

The aim of this study was to investigate the relationship between BDNF and lactate concentration, considering genotype (Val66Met polymorphism) and biological sex, before and after a submaximal graded exercise test.

2 | Materials and Methods

2.1 | Study Design

A pre-post observational study design was used to explore the change in, and correlation between, BDNF and lactate concentration before and after a submaximal graded exercise test in a healthy adult population. Ethics approval was obtained from Royal Prince Alfred Hospital Human Research Ethics Committee (X21-0432), Royal Rehab Research Governance Office (2021-ETH12179) and Australian Catholic University Human Research Ethics Committee (2022-2698RC).

2.2 | Setting

This study was conducted in the exercise research laboratory at Australian Catholic University, Strathfield, NSW, Australia. Data were collected between June and July 2023.

2.3 | Participants

Healthy adult participants were eligible for this study if they: were aged ≥ 18 years, understood written and verbal English language, and were cleared to participate in a submaximal graded exercise text using the Exercise and Sport Science Australia (ESSA) Adult Pre-Exercise Screening System tool (Exercise and Sports Science Australia 2019). Adults were excluded if they had a diagnosis of blood-borne infectious disease and/or diagnosis of other condition(s), acute or chronic, that may limit their ability and safety to participate (e.g., unstable cardiovascular disease). Convenience sampling was used in the study, with participants recruited via social media (e.g., Facebook, LinkedIn, Twitter/X) and via the personal and professional networks of the research team due to the implications of the COVID-19 pandemic limiting active recruitment in research projects in Australia (Villarosa et al. 2021).

2.4 | Exercise Protocol

Heart rate, blood pressure and oxygen saturation were measured before the warm-up and cool-down. All participants completed a submaximal graded exercise test on an upright cycle ergometer (Monark Ergomedic 828E) (Yates et al. 2004). Participants completed a three-minute warm-up of cycling at a comfortable pace prior to commencing the exercise test. During the test, participants were required to cycle at 50–70 revolutions per minute, with the resistance increased by 0.5 kiloponds every three-minutes. Test termination criteria included voluntary cessation of the test, the participant is unable to maintain the required cadence, the participant reaches 90% of age-predicted heart rate maximum or reports near-maximal effort (i.e., 18/20 Rating of Perceived Exertion using the Borg Scale (Borg 1970)), or the participant reports angina and/or dyspnoea (Wilson and Jones 1989). Participants completed a three-minute cool-down (i.e., cycling with zero resistance at a slow cadence) immediately following collection of the post-exercise blood samples. Heart rate (Polar H10 heart rate sensor), blood pressure (WelchAllyn with Littmann Classic III stethoscope), oxygen saturation (Fingertip Pulse Oximeter), and Rating of Perceived Exertion (Borg 1970) were measured in the last 15-seconds of each three-miniute stage.

2.5 | Blood Collection and Analysis

Venous blood samples were collected immediately at pre- and post-exercise to quantify BDNF concentration. Significant reductions in BDNF concentration are observed after 10 to 15-minutes of rest following the cessation of a ramp protocol (Rojas Vega et al. 2006); therefore, in this study, venous and fingerprick blood samples were collected immediately following test completion. An additional venous blood sample was collected pre-exercise to identify the presence or absence of the Val66Met polymorphism. Fingerprick blood samples were collected immediately pre- and post-exercise to quantify lactate concentration. Venous blood collection was carried out by a trained phlebotomist, and fingerprick samples were collected by an ESSA-accredited exercise physiologist.

BDNF concentration was analyzed from the venous serum samples collected using the Enzyme-Linked Immunosorbent Assay (ELISA) method (ab212166, Abcam, Cambridge, MA), reported as nanogram per milliliter (ng/mL). All samples from a given participant were analyzed in duplicate, on the same plate, and all samples were analyzed on the same day. ELISA kit sensitivity was 15.6–1000 picogram per milliliter (pg/mL), with an intra-assay coefficient of variation reported by the manufacturer as

2.8% and inter-assay coefficient of variation of 5.3%. BDNF genotype was detected by TaqMan genotyping probe assay using the QuantStudio 3 System. Samples with the wild type nucleotide G in position 196 (c.196G) were reported as "without the Val66Met polymorphism". Samples that were heterozygous c.196G>A or homozygous c.196G>A were reported as "with the Val66Met polymorphism". Lactate concentration was analyzed from fingerprick blood samples using the Lactate Pro 2 Analyzer (LP2: Arkray, Kyota, Japan) reported as millimole per liter (mmol/L).

2.6 | Statistical Analysis

To detect a moderate change in BDNF concentration with 80% power, a minimum of 24 participants was required. Power calculations, using G*Power software, to detect correlations with a significance level of 0.05, 80% power, and a medium effect size of 0.3, estimated that a sample size of 64 was required. As a result of the COVID-19 pandemic and immediate shutdown, and then ongoing limitations of face-to-face research within Australia (Villarosa et al. 2021), it was not possible to recruit this number of participants, and therefore the correlational analysis for the secondary aim of this study is underpowered. Participants demographic data were tested for normality and presented as mean and standard deviation, frequency and percentage where appropriate. Not-normally distributed data were presented as median and interquartile range. Change in concentration (i.e., BDNF and lactate pre- and post-exercise) was calculated by subtracting the pre-exercise concentration from the post-exercise concentration. Two-sided paired sample T-tests were used to determine the significance of the change in BDNF and lactate concentrations.

Pearson's correlation coefficient (r) was used to examine the relationship between BDNF and lactate concentrations pre- and post-exercise, and between the change scores (i.e., pre- to post-exercise) of both biomarkers (Akoglu 2018). Pearson's correlation coefficient (r) was also used to identify the relationship between BDNF and lactate when accounting for BDNF genotype (i.e., with or without the Val66Met polymorphism) and biological sex (i.e., male or female) (Akoglu 2018). A perfect correlation was taken at ±1.0, a very strong correlation between ±0.8 and ±0.9, a moderate correlation between ±0.6 and ±0.7, a fair correlation between ±0.3 and ±0.5 and a poor correlation between ±0.1 and ±0.2 (Akoglu 2018). Scatterplots were used to visually examine the nature of the relationships between the BDNF and lactate concentrations. Subgroup analyses were conducted to explore the effect of BDNF genotype and sex on the concentration and correlation of BDNF and lactate. One-way ANOVA were conducted to explore the effect of potential confounders on the change in BDNF and lactate concentrations following the exercise protocol. Significance was set at $p < 0.05$. All analysis was conducted in SPSS (IMB SPSS Statistics, version 29.0.1.0).

3 | Results

3.1 | Participant Demographics

Thirty-one healthy adults (17 females) aged 37.5 ± 14.0 years were recruited to this study. Eleven participants (7 females) were identified as carrying the Val66Met polymorphism. Participant characteristics are presented in Table 1.

3.2 | BDNF and Lactate Concentrations

Table 2 presents BDNF and lactate concentrations before and after the submaximal graded exercise test. In the sample of 31 participants, there was a significant increase ($p < 0.001$) in BDNF and lactate concentration from pre- (15.46 ± 3.89 ng/mL and 2.52 ± 0.92 mmol/L, respectively) to post-exercise (17.74 ± 3.92 ng/mL and 11.17 ± 3.34 mmol/L, respectively).

TABLE 1 | Participant demographics. Values presented as mean ± standard deviation or frequency (percentage).

Characteristics	All participants ($n = 31$)	Female participants ($n = 17$)	Male participants ($n = 14$)
Age (years)	37.52 ± 14.02	37.82 ± 14.23	37.14 ± 14.28
Sex (F)	17 (54.8)	17 (100)	14 (100)
BMI (kg/m^2)	24.33 ± 3.27	23.11 ± 2.72	25.82 ± 3.35
VO_{2peak} (mL.kg.m^2)	43.0 ± 10.90	38.00 ± 6.84	49.07 ± 12.01
Val66Met polymorphism	11 (35)	7 (41.2)	4 (28.6)

Note: Values are mean ± standard deviation or frequency (percentage).
Abbreviations: BMI, Body Mass Index; F, female; $VO2_{peak}$, Highest oxygen uptake achieved in the test.

TABLE 2 | Neuroplasticity biomarkers before and after a submaximal graded exercise test.

Biomarker	Pre-exercise (mean ± SD)	Post-exercise (mean ± SD)	Change (post-exercise minus pre-exercise) (mean (95% CI))
BDNF (ng/mL)	15.46 ± 3.89	17.74 ± 3.92	1.95 (1.21–3.35)
Lactate (mmol/L)	2.52 ± 0.92	11.17 ± 3.34	8.7 (7.42–9.90)

Abbreviations: BDNF, Brain-Derived Neurotrophic Factor; CI, confidence interval; mg/mL, milligrams per milliliter; mmol/L, millimoles per liter; SD, standard deviation.

3.3 | Relationship Between BDNF and Lactate Concentrations

Within the full sample, no correlation was identified between BDNF and lactate concentration at pre-exercise ($r = -0.256$, $p = 0.164$) or post-exercise ($r = 0.112$, $p = 0.549$). No correlation was observed between the change (post- minus pre-exercise) in concentration of BDNF and lactate ($r = 0.019$, $p = 0.921$). Figure 1 presents scatterplots showing the relationship between BDNF and lactate concentration before (A) and after exercise (B), and in the change score (C). A poor, non-significant correlation was observed at both time points, and when examining the change scores of both biomarkers.

3.4 | Subgroup Analyses

Subgroup analyses were conducted to explore the effect of potential confounders of BDNF and lactate on the relationship between the BDNF and lactate.

3.4.1 | Val66Met Polymorphism

There was a significant increase in BDNF from pre- to post-exercise in participants with ($n = 11$, mean 2.39 ng/mL, 95% CI 0.67–4.11 ng/mL, $p = 0.011$) and without ($n = 20$, mean 2.22 ng/mL, 95% CI 0.74–3.70 ng/mL, $p = 0.005$) the Val66Met polymorphism. Similarly, there was a significant increase in lactate concentration in participants with ($n = 11$, mean 9.30 mmol/L, 95% CI 6.56–12.04 mmol/L, $p < 0.001$) and without the Val66Met polymorphism ($n = 20$, mean 8.31 mmol/L, 95% CI 6.90–9.71 mmol/L, $p < 0.001$). There was no difference in BDNF and lactate concentrations pre- or post-exercise, or in the change scores when comparing participants with and without the Val66Met polymorphism.

In participants with the Val66Met polymorphism, a moderate, significant inverse correlation was observed between BDNF and lactate concentrations pre-exercise ($r = -0.744$, $p = 0.009$). No significant correlation was observed post-exercise ($r = 0.200$, $p = 0.555$) and when comparing the change from before to after exercise between both biomarkers ($r = -0.121$, $p = 0.722$). No significant correlation was also observed between BDNF and lactate concentration in participants without the Val66Met polymorphism before and after exercise, and when comparing the change in concentration.

3.4.2 | Biological Sex

In female participants, there was a significant increase in lactate in response to the exercise test ($n = 17$, mean 9.04 mmol/mL, 95% CI 7.47–10.60 mmol/mL, $p < 0.001$), but not BDNF concentration ($p = 0.147$). There was also a significant increase in BDNF ($n = 14$, mean 3.59 ng/mL, 95% CI 2.55–4.63 ng/mL, $p < 0.001$) and lactate ($n = 14$, mean 8.2 mmol/mL, 95% CI 5.99–10.41 mmol/mL, $p < 0.001$) concentrations in male participants. There was no difference in BDNF concentrations before ($p = 0.328$) or after exercise ($p = 0.477$) when comparing female and male participants. A significant difference was observed between females and males when comparing the change in BDNF concentration (1.21 ± 3.26 ng/mL vs. 3.59 ± 1.8 ng/mL, $p = 0.016$). No statistical difference in lactate concentration was observed between female and male participants before or after exercise, or in change in lactate.

No correlation was observed between BDNF and lactate concentration in females before or after exercise, or when comparing the change in concentration. However, a moderate, significant inverse correlation was observed between BDNF and lactate concentrations in males pre-exercise ($r = -0.695$, $p = 0.006$). No correlation was observed between BDNF and lactate post-exercise ($r = 0.207$, $p = 0.477$) or when comparing the change in concentration between BDNF and lactate in the male participants ($r = 0.083$, $p = 0.779$).

3.4.3 | Other Potential Confounders

Table 3 presents the ANOVA results for age (Erickson et al. 2010; Begliuomini et al. 2007; Lasek-Bal et al. 2015), body mass index (Begliuomini et al. 2007), depression (Begliuomini et al. 2007; Sen et al. 2008), and physical activity levels (Knaepen et al. 2010). No significant effect was identified for any confounder on change in BDNF nor lactate concentration. Information regarding menstrual cycle phase and training status was collected within this study; however, due to the small sample size, subgroup analyses using this data could not be completed.

4 | Discussion

In this pre-post observational study involving a mixed cohort of healthy adults, no correlation between BDNF and lactate concentration was observed before or after a graded exercise test, or when comparing the change in blood biomarker concentration from pre- to post-exercise. Novel exploratory subgroup analyses identified a moderate inverse correlation between BDNF and lactate concentrations in participants with the Val66Met polymorphism ($r = -0.744$, $p = 0.009$) and in males ($r = -0.695$, $p = 0.006$) at pre-exercise.

Previous research has found an inverse relationship between the change in BDNF and lactate concentrations following an acute bout of high intensity interval training (Antunes et al. 2020) and a graded exercise test (Ferris et al. 2007). This contrasts with the findings of this study. Differences in the characteristics of the study participants may at least partly explain the lack of a correlation observed in this study. This current study comprised more female than male participants, and participants were older compared to previous studies (Antunes et al. 2020; Ferris et al. 2007). Male adults are demonstrated to have higher serum BDNF concentrations at baseline and following an acute bout of moderate intensity aerobic exercise compared to female participants (Bugge Kambestad et al. 2023). While we can only speculate as to the mechanistic underpinnings of the observed sex difference in BDNF concentration, it has been proposed that hormonal changes associated with the menstrual cycle may alter BDNF concentration (Begliuomini et al. 2007). The mean age of participants in this study (37.52 ± 14.02 years) is slightly greater than the mean age of participants in previous studies exploring the correlation between BDNF and lactate concentration (28.8 ± 5.6 years (Martland et al. 2020) or 25.4 ± 1.01 years (Ferris

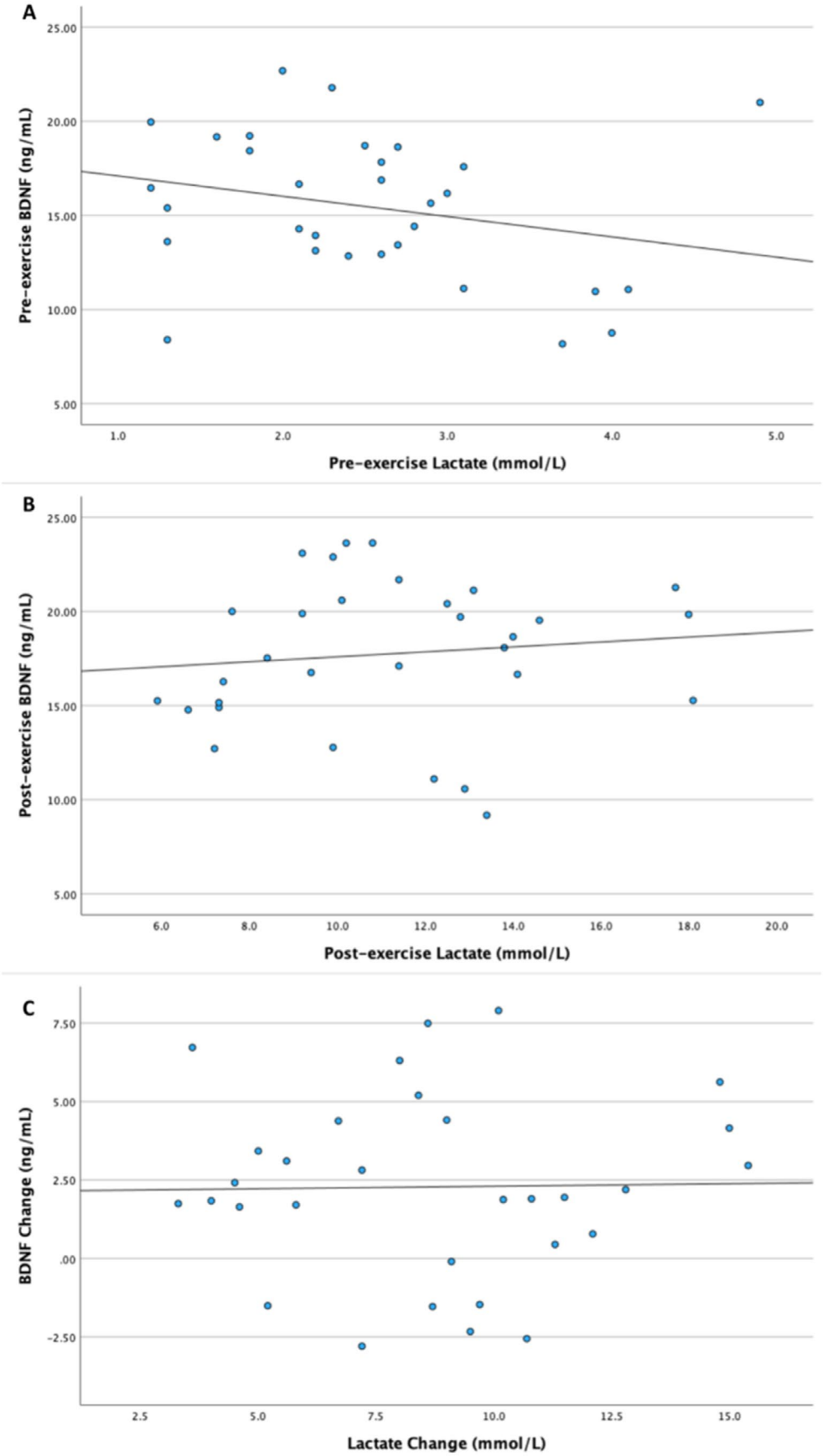

FIGURE 1 | Scatterplot of the relationship between BDNF and lactate at pre-exercise (A), post-exercise (B), and change in concentration (post-minus pre-exercise) (C).

TABLE 3 | Effect of potential confounders on change in BDNF and lactate concentration.

	Change in BDNF concentration	Change in lactate concentration
Age (years)	$F(1, 29) = 0.050$, $p = 0.825$	$F(1, 29) = 1.879$, $p = 0.181$
BMI (kg/m^2)	$F(1, 29) = 0.385$, $p = 0.540$	$F(1, 29) = 0.357$, $p = 0.55$
Depression (DASS)	$F(1, 29) = 0.123$, $p = 0.728$	$F(1, 29) = 2.535$, $p = 0.122$
Weighted exercise per week (min/week) (ESSA APSS, version 2, 2019)	$F(1, 29) = 0.343$, $p = 0.564$	$F(1, 29) = 2.984$, $p = 0.095$
VO_{2peak} (mL.kg.m^2)	$F(1, 29) = 2.874$, $p = 0.101$	$F(1, 29) = 0.018$, $p = 0.895$

Note: Weighted exercise = (minutes of light exercise + minutes of moderate exercise) + (2 × minutes of vigorous/high exercise).
Abbreviations: BMI, Body Mass Index; DASS, Depression Anxiety Stress Scales; ESSA APSS, Exercise and Sports Science Australia Adult Pre-Exercise Screening System.

et al. 2007)). Therefore, the inclusion of female and older participants may have impacted BDNF concentration, and therefore the correlation between BDNF and lactate. There is evidence to suggest that BDNF concentration declines with age (Erickson et al. 2010; Lommatzsch et al. 2005; Ziegenhorn et al. 2007), but this study is unable to determine the effect of age on the relationship between BDNF and lactate.

This study is the first to examine the relationship between BDNF and lactate while accounting for sex and the Val66Met polymorphism, and key confounders of BDNF concentration. These findings suggest that lactate and BDNF should not be used interchangeably as markers of neuroplasticity, though increased lactate concentration may signal an increase in BDNF. Other studies found no relationship between the presence of the Val66Met polymorphism and BDNF concentration in healthy adults (Bugge Kambestad et al. 2023; Helm et al. 2016), however, a significant interaction was evident between BDNF concentration and biological sex after exercise (Bugge Kambestad et al. 2023). The study conducted by Helm and colleagues (2017) did not report the sex of participants, which may be associated with the lack of correlation identified between BDNF and lactate concentrations reported in the mixed-sex cohort (Helm et al. 2016). Therefore, biological sex should be considered when examining BDNF concentration, and the subsequent correlation between BDNF and lactate concentration. However, these findings should be interpreted with caution due to the small sample and need to be validated in larger studies.

It is unclear whether the increase in lactate following high intensity exercise directly increases BDNF concentration or is due to other associated processes (e.g., changes in pH and blood gases) (Schiffer et al. 2011). Therefore, lactate has been referred to as a 'pseudo-hormone' that facilitates the upregulation of BDNF secretion following exercise (Schiffer et al. 2011). Pre- and post-exercise levels of BDNF concentration among the male participants within the current study were higher than those of existing literature (Antunes et al. 2020). This difference may be attributed to potential confounders such as diet (e.g., higher carbohydrate load) (Andersen et al. 2013), excessive muscle work (e.g., asthma) (Appel et al. 1983), and consumption of alcohol (MacDonald et al. 1994) which were not examined within the current study. Lactate and gas exchange thresholds occur at higher percentages of maximal oxygen uptake for women than men, therefore women may have lower metabolic stress and lactate concentrations than male participants (Meyler et al. 2021). Further exploration into the effect of confounding variables on lactate concentration is necessary to determine their effect on BDNF concentration and subsequently the relationship between BDNF and lactate at various timepoints.

4.1 | Limitations

Challenges in recruitment largely due to the COVID-19 pandemic impacted the planned recruitment strategies for this study and resulted in the secondary correlational analyses being underpowered to observe an effect in the correlational analysis. However, we have reported the outcomes of this analysis as the preliminary findings can provide an insight into the potential relationships between BDNF and lactate concentration and age, and sex of the study participants. Secondly, a convenience sample recruited via social media and professional networks was used in this study which may have introduced selection bias. Future studies should employ more rigorous sampling methods, such as random sampling, to improve the heterogeneity of the sample and increase the validity and robustness of the research findings and the generalizability of the results.

Thirdly, the effects of additional potential confounders to BDNF and lactate concentrations, and subsequently the correlation between these variables, were unable to be explored with adequate power. Fitness level (Knaepen et al. 2010) and phase of menstrual cycle of female participants (Begliuomini et al. 2007) were collected, however the sample size was too small to allow these analyses to be run. Time to maximal lactate steady-state (Faude et al. 2017), diet (Andersen et al. 2013), and consumption of alcohol (MacDonald et al. 1994) were not measured, and their effect on the results of this study are unknown. Despite using age-predicted heart rate maximum and Rating of Perceived Exertion as testing cut-offs within the exercise protocol, participant fitness levels may have impacted the BDNF and lactate concentrations obtained. Participants in the current study recorded a lower maximal oxygen uptake and achieved a lower predicted peak power output compared to previous research (Rojas Vega et al. 2006). However this test was conducted until exhaustion and in a male only cohort (Rojas Vega et al. 2006). Therefore, future studies are needed to explore the impact of additional potential confounders and different training conditions (e.g., high intensity interval training) or time post-exercise (e.g.,

every five-minutes for 15-minutes) (Rojas Vega et al. 2006) on the BDNF and lactate concentrations of healthy adults.

5 | Conclusion

The findings of this pre-post observational study suggest that BDNF and lactate concentrations are not correlated before or after exercise, or when comparing changes in concentration in healthy adults, using the exercise test and blood sampling protocol described. Preliminary exploration of the relationship between BDNF and lactate before and after the exercise protocol while accounting for the presence of the Val66Met polymorphism and biological sex indicated an effect at pre-exercise only. While BDNF and lactate concentrations are responsive to increasing exercise intensity in a healthy population, lactate cannot be used as an alternative to BDNF and subsequently may not be an indication of BDNF-associated neuroplasticity.

Author Contributions

S. K. Ashcroft: conceptualization, data curation, formal analysis, funding acquisition, investigation, methodology, project administration, visualization, supervision, writing – original draft. **K. Basclain:** methodology, investigation, formal analysis, validation, writing – review and editing. **C. Woolnough:** methodology, investigation, formal analysis, validation, writing – review and editing. **M. W. Hoon:** investigation, methodology, writing – review and editing. **S. J. Walsh:** investigation, methodology, writing – review and editing. **L. C. Starc:** investigation, methodology, writing – review and editing. **L. Johnson:** conceptualization, data curation, formal analysis, funding acquisition, investigation, methodology, supervision, visualization, writing – original draft. **S. S. Kuys:** conceptualization, data curation, formal analysis, funding acquisition, investigation, methodology, supervision, visualization, writing – original draft. **A. G. Thompson-Butel:** conceptualization, data curation, formal analysis, funding acquisition, investigation, methodology, supervision, visualization, writing – original draft.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Raw data can be accessed via communication with the corresponding author.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.