8-2022

Exploring Sex Differences in the Effect of Cannabidiol on Physical Activity, Cognition, Psychological Wellbeing, and Inflammatory and Neural Health Biomarkers

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EXPLORING SEX DIFFERENCES IN THE EFFECT OF CANNABIDIOL ON PHYSICAL ACTIVITY, COGNITION, PSYCHOLOGICAL WELLBEING, AND INFLAMMATORY AND NEURAL HEALTH BIOMARKERS

A Dissertation Submitted in Partial Fulfillment
of the Requirements for the Degree of
Doctor of Philosophy

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College of Natural Health Sciences
School of Sport and Exercise Science
Exercise Physiology

August 2022

This Dissertation by: Victoria Flores

Entitled: *Exploring Sex Differences in the Effect of Cannabidiol on Physical Activity, Cognition, Psychological Wellbeing, and Inflammatory and Neural Health Biomarkers*.

has been approved as meeting the requirement for the Degree of Doctor of Philosophy in College of Natural Health Sciences in School of Sport and Exercise Science, Program of Exercise Physiology.

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ABSTRACT

Flores, Victoria. *Exploring sex differences in the effect of cannabidiol on physical activity, cognition, psychological wellbeing, and inflammatory and neural health biomarkers.* Published Doctor of Philosophy dissertation, University of Northern Colorado, 2022.

Cannabidiol (CBD) is believed to improve physical and mental health in recreationally active men and women. The purpose of this study was to investigate the biological sex-related differences in physical activity, health-related fitness, mental and cognitive health, and biomarkers of inflammation and neural health before and after an 8-week CBD intervention.

Participants (N =49; CBD Treatment Group (CG): n =24; Placebo Treatment Group (PG): n = 25; Females: n = 25; Males: n = 24; Males in CBD Group (CF-M): n = 12; Females in CBD Group (CG-F), n = 12; Males in Placebo Group (PG-M): n =12; Females in Placebo Group (PG-F): n = 13) completed a total of 8 visits, separated by an 8-week intervention period of either 50 mg of CBD or a calorie-matched placebo to consume daily. Before and after the intervention, participants completed a fasted blood draw, psychological and cognitive function questionnaires, and assessments for body composition, peak oxygen uptake, anaerobic fitness, and muscular strength. Isolated serum was used to determine resting concentrations of C-reactive protein (CRP) and brain-derived neurotrophic factor (BDNF) using enzyme-linked immunoassays. Data were analyzed with SPSS using independent t-tests and 2 and 3-way mixed analysis of variance ($\alpha = 0.05$).

An interaction (time*treatment) on anaerobic fitness was found in which PG experienced a 9% and 3% decline in mean peak power ($p = 0.006$) and relative peak power ($p = 0.006$)

compared with CG. Another interaction (treatment*sex) was found on overall CRP concentrations in which CG-F had 92% and 115% greater overall mean CRP concentrations than PG-F ($p = 0.026$) and CG-M ($p = 0.012$), respectively. Another interaction (treatment*sex) was also found on overall BDNF concentrations in which PG-F had 43% and 39% greater overall mean BDNF concentrations than CG-F ($p = 0.014$) and PG-M ($p = 0.008$), respectively.

Results suggest that 8 weeks of CBD does not alter body composition, cardiorespiratory fitness, and muscular strength. However, results suggest that it may serve as a potential aid in preventing decreases in anaerobic fitness, and that its effect on resting concentrations of CRP and BDNF are different between males and females.

ACKNOWLEDGEMENTS

My dissertation would not have been possible without the support of others. First and foremost, I want to thank my Lord and Savior, Jesus Christ, for this opportunity to grow into who I am and where I am today.

I would like to thank my mentor, Dr. Laura Stewart, who has guided me, taught me more than academic-related lessons, and expanded my thoughts with insights and solutions. Without your mentorship, I really do not know where I would be, other than frustrated and lost in my own thoughts! Your guidance and welcoming demeanor for anything I was experiencing taught me perspective and that it was okay to be vulnerable and imperfect, and that I can and will survive. You made it so easy for me to open up to you about my feelings with imposter syndrome, self-doubt, etc, and I am so thankful for the way you listened and encouraged me through. I would not have gotten this far without you believing in me and giving me words of affirmation. I also thank you for giving the chance to work with your lab. The trials and tribulations of switching a dissertation project and bouncing back from numerous, failed ELISAs has also helped me develop resilience, and for that, I am truly grateful. I now know how to handle myself in these dilemmas. I hope to one day emulate your amazing mentorship and tell you about all the positive effects it has had in my journey with others.

I am extremely thankful to my committee members for their support, encouragement, and provisions. Thank you, Dr. David Hydock, for helping me refine my methods with the $\dot{V}O_2$ peak protocol and helping me consider other myokines as well as the sex and gender spectrum. I am particularly grateful for the space you provided me during office and lab visits--your consistent

encouragement through application processes and data collection was comforting and reassuring to me. Thank you, Dr. Mark Thomas, for your expertise and direction in helping me understand central and peripheral BDNF concentrations as well as its relationship with CBD. I also want to thank you for the laughs and conversations in and out of class--those enjoyable tidbits put me at ease during a stressful time and reminded me that academia is just one aspect of life. Thank you, Dr. James Haughian, for your patience and advice in helping me see how my work can have real-life applications to other populations. I can recall your words (and an exam question!) that as scientists, we should be able to explain our research simply to others. I want you to know that that concept has made a deep impression on me.

I am so thankful for the University of Northern Colorado, the Graduate School, and the departments I was able to work with. All the GSA student research grants and NHS student research funds afforded me flexibility in making this project happen, thank you so much David Shimokawa and Dr. Kim Murza. Thank you, Dr. Gary Heise, for those small check-ins about how data collection is going and for trusting me with teaching an array of classes within SES. I am deeply grateful for all the help M'lyn Miller has given me--the countless numbers of times I stopped by your office and asked for your assistance, thank you! I am grateful for Dr. Cindy Wesley and Dr. Jeri Lyons. Thank you for the opportunity to be a part of the 3 Minute Thesis Challenge, to be a speaker for Zoom conferences during the pandemic, and the opportunity to apply to the Distinguished Dissertator Fellowship. These experiences have been monumental in my doctoral student journey, and I am so grateful to take part in these opportunities. Lastly, I am deeply grateful for my experience with University 101 under Dr. Angela Vaughan's supervision. This teaching experience changed my life and how I will teach, forever. Words cannot express how appreciative I am to have been a part of your team and learn how to best serve students.

To my family, I am so blessed to have you complete this chapter with me. I am so extremely thankful to God for giving me such hard-working and fiercely loving parents. Thank you, mom and dad, for working so incredibly hard to send me to college, for your unwavering support, unconditional love, comfort and provisions, and believing in me. I am sure it wasn't easy seeing your youngest relocate to another state and pursue our family's highest degree; thank you for letting me do this and being right behind me. I am deeply appreciative of my siblings: Shaun, for your financial advice and mental support when I needed it the most, Yvette, for Facetime chats about family and life reflections, and Lisa, for provision and safety support.

I would like to express my deepest gratitude to the amazing friends I have made. Thank you, Dr. Joshua Cotter, for staying in touch with me, especially when I wasn't the most responsive! Thank you to my colleagues, lab team, bible study group, and thank you to the other amazing individuals I met along the way in this walk of life. To my hard-working and hilarious lab mates Jake, Arj, Ryland, Eddie, Keola and Seth: thank you for helping me with data collection and being so fun to work with. To my (past and present) colleagues Blake, Salah, Jonny, Peter, Nate, Nick, Luke, Lea, Brandon, Tyler, Buck, Zac, Dani, Francis, Tsung-Lin: thank you for being so kind to me, being a source of both inspiration and relaxation for me despite the challenges we've each been through and continue to work through. To my Uni 101 crew: Angela, Mike, and my students who've kept in touch with me since our Fall 2018 start together at UNC: I am so incredibly lucky to have an ongoing friendship beyond our semester together. To my bible study friends Alicia, Josh, Sami, Connor, Alaina, Delaney, Marissa, and Tyler: thank you for your fellowship, spiritual support, and unconditional love. There are simply too many of you whom I have specific, fond memories of and I am so fortunate to have had

experiences with you all. You all were crucial to my health and wellbeing at the University of Northern Colorado and I would not have been able to finish strong without you.

I cannot begin to express my sincere appreciation to my partner, Attila, and the Lassu family who provided me emotional support and a place to stay all these years during my time at UNC. Thank you for your care and inspiration during my deepest frustrations, and for your love and assistance with my late nights and moments of despair. Thank you so much, Attila, for helping me study, taking care of my car, preparing and being there with me for my bodybuilding shows, driving me to and from the airport on multiple occasions, feeding me during busy times, exercising with me to keep me accountable, encouraging me through my most insecure times at school, lab, and home, and accepting me for who I am without any questions or doubt. I am so thankful for you and hope to be there for you always to return the countless favors you've done for me out of your love and kindness.

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LIST OF ACRONYMS

1RM	One repetition maximum
2-AG	2-arachidonoylglycerol
ACSM	American College of Sports Medicine
AEA	N-arachidonoyl-ethanolamine, anandamide
AF	Anaerobic fatigue
AHA	American Heart Association
ANOVA	Analysis of variance
BACS	Brief Assessment of Cognition in Schizophrenia
BDNF	Brain-derived neurotrophic factor
BF%	Body fat percentage
BM	Body mass
BMI	Body mass index
BP	Bench press
BS	Back squat
CB1r	Cannabinoid type 1 receptor
CB2r	Cannabinoid type 2 receptor
CBD	Cannabidiol
CG	Cannabidiol group
CG-F	Cannabidiol group-Females
CG-M	Cannabidiol group-Males

CNS	Central nervous system
CRP	C-reactive protein
CV	Coefficient of variabilities
CVD	Cardiovascular disease
ECS	Endocannabinoid system
ELISA	Enzyme linked immunosorbent assay
ERK	Extracellular signal-regulated kinases
FAAH	Fatty acid amide hydrolase
FDA	Federal Drug Administration
I.p.	Intraperitoneal
IPAQ	International Physical Activity Questionnaire
IFN-γ	Interferon gamma
IL-1ra	Interleukin 1ra
IL-1β	Interleukin 1 beta
IL-6	Interleukin 6
IL-8	Interleukin 8
IL-10	Interleukin 10
IL-13	Interleukin 13
LBM	Lean body mass
LPS	Lipopolysaccharide
MAGL	Monoacylglycerol lipase
MCT	Medium chain triglyceride
mRNA	Messenger ribonucleic acid

mph	Miles per hour
MP	Mean power
MS	Multiple Sclerosis
MVPA	Moderate to vigorous physical activity
NF-κB	Nuclear factor kappa B
NIH PROMIS	National Institute of Health Patient-Reported Outcomes Measurement Information System
NSCA	National Strength and Conditioning Association
PG	Placebo group
PG-F	Females in the placebo group
PG-M	Males in the placebo group
PKB	Protein kinase B, also known as AKT
PP	Peak power
PWB	Psychological wellbeing
RA	Rheumatoid arthritis
RDBP	Resting diastolic blood pressure
RHR	Resting heart rate
RMP	Relative mean power
RPP	Relative peak power
RSBP	Resting systolic blood pressure
SST	Serum separator tube
TNF-α	Tumor necrosis factor α
TrkB	Tropomyosin receptor kinase B

USG	Urine specific gravity
$\dot{V}O_{2\ peak}$	Peak oxygen uptake

CHAPTER I

INTRODUCTION TO THE STUDY

Chronic inflammation is defined as inflammation lasting for prolonged periods of time and is correlated with many negative health outcomes, such as loss of cognitive function, development of fatigue and depression, and increased mortality rates (Jehn et al., 2015; Kumari et al., 2016). In clinical situations, the inflammatory status of an individual may be determined by monitoring measurements of peripheral concentrations of the inflammatory biomarkers interleukin-6 (IL-6) and C-reactive protein (CRP) in blood (C. H. Liu et al., 2017). Interleukin-6 is most well-known for the regulation of local inflammation which often involves the production and recruitment of leukocytes and acute-phase response proteins (Murphy & Weaver, 2017). C-reactive protein is an acute-phase protein synthesized in the liver during inflammation and assists in acute infection or injury by opsonizing contaminants or agents (Murphy & Weaver, 2017). Normal concentrations of serum and plasma IL-6 and CRP can vary depending on age (Stewart et al., 2007), acute infection (Thompson et al., 1999), and health and disease status (Marzolini et al., 2020). Typically, IL-6 concentrations are within 0.9-3 pg/mL (Herder et al., 2007; Maachi et al., 2004) and CRP concentrations are around 6 mg/L (Marzolini et al., 2020) in those with chronic inflammation such as obesity, and $\leq$ 1.8 pg/mL and <3 mg/L, respectively, in healthy individuals (Libardi et al., 2012; Ridker, 2003).

Neuroinflammation, which is defined as inflammation in the brain and spinal cord, is mediated by microglia, which is an innate cytokine-producing immune cell in the central nervous system (CNS; Lenz & Nelson, 2018). In chronic neuroinflammatory conditions, microglia

release pro-inflammatory cytokines including IL-6, interleukin-1 beta (IL-1β), interferon gamma, and tumor necrosis factor alpha (TNF-α) which are associated with reduced neuronal plasticity and cognitive impairments (Lenz & Nelson, 2018; C. H. Liu et al., 2017; Mosser & Edwards, 2008). Microglia also release anti-inflammatory cytokines including interleukin-10 (IL-10) and interleukin-13 (IL-13) in periods of early life development, acute growth stress, and exercise. These cytokines assist with tissue growth, remodeling, and repair (Lenz & Nelson, 2018; Littlefield et al., 2015; Lobo-Silva et al., 2016). Microglia also release brain-derived neurotrophic factor (BDNF), a neurotrophin that regulates neuronal development and function (Gomes et al., 2013; Norden et al., 2016). Murine models show that acute activation of microglia cause the release of the anti-inflammatory cytokines IL-10 and IL-13 which will, in turn, act to increase central BDNF secretion resulting in improvements in neuroprotection (Gomes et al., 2013; Lobo-Silva et al., 2016). Conversely, chronic activation of the microglia can cause the release of the pro-inflammatory cytokines IL-6 and others, which can reduce central BDNF secretion resulting in diminished neuroprotection (Gomes et al., 2013). Central BDNF can cross the blood brain barrier and act through autocrine and paracrine mechanisms in peripheral tissues and organs (Pan et al., 1998), and peripheral BDNF can be produced from non-CNS tissues as well (Kerschensteiner et al., 1999; Matthews et al., 2009; Urabe et al., 2013).

Exercise volume, duration, and body composition are factors that influence the relationship among IL-6, CRP, and BDNF. Although IL-6 is pro-inflammatory, its release during exercise has positive effects by upregulating the anti-inflammatory cytokines IL-10 and interleukin-1ra (IL-1ra), and inhibiting TNF-α (Petersen & Pedersen, 2005). Although an acute inflammatory event associated with exercise may be beneficial, chronic low-grade inflammation, such as persistent elevated circulating concentrations of IL-6, can be detrimental. Additionally,

chronic exercise training decreases both IL-6 and CRP concentrations and these decreases are associated with lower risk for cardiovascular disease (CVD; Smith et al., 1999) and hypertension (Smith et al., 1999). Regular physical activity, which is usually measured as daily step counts with an accelerometer, is recognized as a cost-effective and non-pharmaceutical method aimed at reducing IL-6 and CRP concentrations in individuals with disease. Completing more than 5,000 steps per day reduces IL-6 and CRP concentrations in those with obesity (Renault et al., 2017; Zang et al., 2019), autoimmune disorders (Moy et al., 2014), and other inflammatory diseases (Webb et al., 2018). A single bout of exercise also transiently increases BDNF concentrations (Briken et al., 2016; Cabral-Santos et al., 2016; Castellano & White, 2008), but other research shows that chronic exercise training increases resting BDNF concentrations (Erickson et al., 2011; Nofuji et al., 2008), or has no effect (Schiffer et al., 2009).

Brain-derived neurotrophic factor and its relationship to inflammatory cytokines also appear to be sex-dependent. Preclinical studies show that female rodents display significantly greater microglial density and heightened microglial activation in the prefrontal cortex when subjected to stress compared to male rodents (Bilbo et al., 2012; Bollinger et al., 2016; L. L. Liu et al., 2019). Female mice also experience significant reductions in hippocampal BDNF messenger RNA (mRNA) expression and these reductions are positively correlated with depressive-like behaviors, and negatively correlated with TNF-α mRNA expression when compared to males (L. L. Liu et al., 2019). Additionally, female mice are thought to be more sensitive to stress than males (L. L. Liu et al., 2019). The relationship among sex, BDNF concentrations, and inflammatory cytokines is thought to be the same in humans, but the relationship has yet to be fully elucidated. Human females demonstrate a significantly greater IL-6 response in stress-evoked situations than males (Lockwood et al., 2016). Neuropsychiatric

research also shows that BDNF concentrations are correlated with IL-6 concentrations in those diagnosed with depression (Patas et al., 2014) and that females are 1.5-2 times more likely to experience mood and anxiety disorders than males (McLean et al., 2011).

Additionally, IL-6 is associated with increased body mass index (BMI) and fat mass as well as elevated abdominal adiposity (Bermudez et al., 2002; Festa et al., 2001; Lear et al., 2003; Rexrode et al., 2003). Greater central abdominal adiposity is significantly linked to elevated IL-6 and CRP concentrations more so in females, even after accounting for other lifestyle factors including physical activity, smoking, or alcohol intake (Thorand et al., 2006). Overweight and obese women also have 25% higher serum BDNF concentrations compared to overweight and obese men (Glud et al., 2019). These findings suggest that women may experience differences in the degree of BDNF expression related to higher fat mass and central adiposity. However, the relationship between BDNF and inflammatory cytokines has not been fully explored and it is possible that high concentrations of systemic IL-6 and CRP can affect neural health differently in each sex.

Cannabidiol (CBD), the non-psychoactive phytocannabinoid contained in *Cannabis sativa L.*, has become a popular supplement marketed with claims to help control chronic inflammation and neuroinflammation. Cannabidiol is most recognized as a potential treatment for neuroinflammatory diseases and disorders including models of depression (Gáll et al., 2020; Maroon & Bost, 2018; Premoli et al., 2019; Sales et al., 2019, 2020; Silote et al., 2019; Solowij et al., 2018), anxiety (Gáll et al., 2020; Maroon & Bost, 2018; Premoli et al., 2019; Solowij et al., 2018), Parkinson's Disease (Peres et al., 2018), Alzheimer's Disease (Peres et al., 2018; Premoli et al., 2019), and a variety of cancers (Maroon & Bost, 2018). In fact, CBD is approved by the United States Food and Drug Administration (FDA) for the treatment of two severe forms of

epilepsy (Khan et al., 2018; Maroon & Bost, 2018; Premoli et al., 2019). Cannabidiol regulates inflammation through mechanisms involving the endocannabinoid system (ECS) which consists of the cannabinoid type 1 receptors (CB1r) and cannabinoid type 2 receptors (CB2r), and the endocannabinoids *N*-arachidonoyl-ethanolamine, also known as anandamide (AEA), and 2-arachidonoylglycerol (2-AG; Di Marzo, 2018; Fine & Rosenfeld, 2013). Cannabidiol is a negative allosteric modulator of human CB1r (Laprairie et al., 2015) and has a higher affinity to CB2r (Tham et al., 2019). The anti-inflammatory effects of CBD are recognized by its antagonistic effect on CB2r in various human cells (Couch et al., 2017; Muthumalage & Rahman, 2019; Petrosino et al., 2018). For example, CBD reduced the production of IL-6, TNF-α, and the chemokines involved in the recruitment of macrophages in human keratinocytes exposed to allergens (Petrosino et al., 2018), and in macrophages and fibroblasts stimulated with lipopolysaccharide (LPS; Muthumalage & Rahman, 2019). Cannabidiol was found to increase endogenous AEA concentrations which, in turn, acted on immune cells through CB2r which resulted in the downregulation of leukocyte pro-inflammatory cytokine release (Petrosino et al., 2018; Turcotte et al., 2016).

Preclinical studies illustrate that CBD may also mediate neuroinflammation and brain health as measured by changes in BDNF concentrations. The evidence from animal studies is convincing. For example, in mice with induced brain ischemia, 3 weeks of intraperitoneal (i.p.) CBD injections decreased hippocampal neurodegeneration and improved hippocampal BDNF concentrations (Mori et al., 2017). In a separate study, which used a murine model of Alzheimer's Disease, a 24-hour repeated i.p. CBD treatment reduced neuroinflammation from astrocytes and promoted neurogenesis in injured hippocampi (Esposito et al., 2011). Lastly, a single dose of i.p. CBD attenuated IL-6 and TNF-α production and also attenuated decrements in

hippocampal BDNF concentrations and cognitive impairment in mice that underwent bacterial inoculation (Barichello et al., 2012).

Clinical studies also suggest that CBD treatment positively affects brain function and neuroinflammation. For example, one dose of oral CBD attenuated intravenous THC-induced psychosis and striatal and amygdala activation during a fearful visual stimulation task in healthy men (Bhattacharyya et al., 2010). In the same study, the CBD-only group also performed better during the verbal recall test compared to the THC and placebo-only groups (Bhattacharyya et al., 2010). Clinical studies also demonstrate that CBD treatment improves psychotic symptoms in psychiatric patients (Shannon et al., 2019), anxiety in patients with post-traumatic stress disorder (Elms et al., 2019), and general anxiety disorder (Bergamaschi et al., 2011). Given that CBD improves these outcomes, CBD may mediate the control of brain function and neuroinflammation in healthy individuals. Although these findings are intriguing, the relationship among CBD, inflammatory cytokines, BDNF, and improved cognitive function is still not clearly understood (Fumagalli et al., 2006; Premoli et al., 2019; Silote et al., 2020).

There is very little information about whether sex plays a role in mediating similar CBD-induced physiological and psychological responses. There are sex-related differences in the inflammatory response and in the degree of muscle damage from eccentric exercise in animals and humans (Komulainen et al., 1999; Stupka et al., 2000), in ECS function in mice and rats (Dow-Edwards, 2020; Fattore & Fratta, 2010), in brain structure and function (Eggers et al., 2014; Kaczkurkin et al., 2019), and in microglial density and stress response (Bollinger et al., 2016). Taken together, males and females may differ in their response to CBD use. This difference may, in turn, affect circulating concentrations of IL-6, CRP, and BDNF as well as brain function and general wellbeing.

Cannabidiol is easily obtainable and marketed as a health supplement for everyday use for people who may not be experiencing neurodegenerative and neuropsychiatric disorders. Unfortunately, many CBD companies rely on anecdotal evidence to support their claims and market their product without knowledge of the full scope of CBD-related physiological and psychological responses. This is surprising given that a study found that 55% of 2,400 medicinal cannabis community members in America used CBD-only products identified as women, and 44% of the CBD-only users identified as men (BrightfieldGroup, 2017). Additionally, no human research exploring the effects of CBD on measures of physical activity and exercise exists. This is alarming because an exercise and cannabis use survey found 70% of 605 respondents use cannabis before working out to make exercise feel more enjoyable (YorkWilliams et al., 2019). This suggests that CBD and THC may induce endorphins, activate opioid receptors, and alter physical activity behavior, but no studies have explored these mechanisms. There are currently no studies investigating sex differences related to CBD, inflammation, and BDNF, and whether CBD may affect cognitive function and wellbeing in physically active and healthy adults.

In summary, healthy individuals who may or may not have inflammation and are recreationally active may experience alterations with CBD use in their overall wellbeing. It is unknown whether these alterations are associated with sex and result in any benefit or harm to the user. There are not enough studies involving healthy men and women to fully understand the relationship among inflammation, physical activity, mental and physical health, and long-term CBD use. This raises the following questions in CBD-related research:

Q1 Is there a difference by sex or by treatment with respect to physical activity patterns, health-related fitness, measures of mental and cognitive health, and concentrations of CRP and BDNF?

Q2 Does 8 weeks of CBD affect physical activity patterns, health-related fitness, measures of cognitive and mental health, and resting concentrations of CRP and BDNF?

More research is needed to match the exponential production and consumption of CBD to help inform both public and health care officials about any potential effects it may have.

Purpose and Hypotheses

The purpose of this double blind, placebo-controlled, clinical trial with parallel group design was to investigate the biological sex-related differences in physical activity patterns, health-related fitness, mental and cognitive health before and after an 8-week CBD intervention. This study also aimed to explore whether 8 weeks of CBD treatment would significantly alter biomarkers of inflammation and neural health. The specific aims for this study were:

A1 Explore potential overall differences at the pre-intervention time point, by sex or by treatment assignment, with respect to physical activity patterns, health-related fitness, measures of mental and cognitive health, and concentrations of inflammatory and neural health biomarkers.

H1 At the pre-intervention time point, females will have lower average daily step counts and distance traveled, lower muscular strength, relative peak oxygen uptake ($\dot{V}O_2$ peak) values, and anaerobic fitness performance measures, higher percent body fat and concentrations of CRP, and similar BDNF concentrations and measures of cognitive function and psychological wellbeing when compared with males.

H2 It was also hypothesized that, when the sexes were combined into treatments of males and females consuming CBD and males and females consuming placebo, those assigned placebo will not be different than those assigned CBD with respect to physical activity patterns, health-related fitness, measures of mental and cognitive health, and concentrations of inflammatory and neural health biomarkers at the pre-intervention time point.

A2 Explore the treatment effects of an 8-week CBD intervention on physical activity patterns, health-related fitness, measures of mental and cognitive health, and concentrations of inflammatory and neural health biomarkers.

H3 Both sexes consuming CBD will experience increases in average daily step counts and distance traveled, decreases in percent body fat, improvements in relative

$\dot{V}O_2$ peak, as well as increases in muscular strength and anaerobic fitness performance measures over the course of the intervention period when compared to those consuming placebo. Both sexes consuming CBD will also experience improvements in cognitive function and psychological wellbeing scores, reduced concentrations of CRP, and an increase in concentrations of BDNF over the course of the intervention period when compared to those consuming placebo.

H4 It was also hypothesized that females consuming CBD will experience a greater increase in average daily step counts and distance traveled, greater reduction in percent body fat, greater improvements in $\dot{V}O_2$ peak, cognitive function, and psychological wellbeing scores, a more significant reduction in concentrations of CRP, and a more significant increase in concentrations of BDNF when compared with males consuming CBD.

CHAPTER II

REVIEW OF LITERATURE

Inflammation

Inflammation is a necessary response elicited by the body to address tissue damage, infection, or injury. The process by which inflammation begins involves the activation and recruitment of macrophages, neutrophils, mast cells, and other leukocytes from the innate or adaptive immune systems. The type of coordinated response is dependent on the distress signals released from immune cells following recognition by pathogen-associated molecular pattern molecules and damage-associated molecular pattern molecules through pattern recognition receptors (Murphy & Weaver, 2017). As inflammation progresses, leukocytes work to repair the damaged area by producing more chemotactic factors that induce unidirectional leukocyte movement to reinforce the inflammatory signal, increase phagocytic activity, and promote degranulation and secretion of precursor zymogens (Murphy & Weaver, 2017). In instances that require a stronger immune response, immune cells will further enhance activation by releasing more pro-inflammatory soluble factors. Acute responses to local inflammation are accompanied by up to 5 main characteristics in the infected area, which include redness, pain, heat, swelling, and immobility, and are dependent on the severity of the inflammatory response (Murphy & Weaver, 2017).

Prolonged activation and recruitment associated with the inflammatory response may lead to chronic inflammation which is defined as inflammation lasting for several months to many years. This maladaptive response results in increased cellular stress and malfunction

(Medzhitov, 2008). This condition is associated with many deleterious health outcomes, including the development and progression of cancer (Li et al., 2020), CVD (Fioranelli et al., 2018), obesity and metabolic diseases (Ramos-Arellano et al., 2020; Zatterale et al., 2020), as well as neuropsychiatric disorders that impact brain function, emotion, and mood. The persistent, low-grade stimulation of the leukocytes and their specific signal-transduction pathways contributes to the phenotypic symptoms experienced in these disorders such as tumor growth (Li et al., 2020), vascular endothelial dysfunction (Fioranelli et al., 2018), mood disorders (M. H. Chen et al., 2021; Wright et al., 2005), and cognitive deficit disorders (Parbo et al., 2017).

Biomarkers of Inflammation

Current research related to the development of therapeutic targets has focused on the potential causes and subsequent signs of chronic inflammation. One of these strategies involves measuring peripheral biomarkers to help gauge the presence and severity of inflammation and determine risk for disease. Elevated circulating concentrations of the biomarker interleukin 6 (IL-6) and its induced protein, C-reactive protein (CRP), are commonly associated with both acute and chronic inflammatory episodes and are used in both clinical and research environments (Murphy & Weaver, 2017).

Interleukin-6 is a member of the hematopoietin superfamily of cytokines which stimulates the production of new monocytes and granulocytes in the bone marrow and plays a crucial role in inducing the acute-phase response in the liver (Murphy & Weaver, 2017). This biomarker is produced by a variety of cells but mostly in macrophages and monocytes in response to inflammation. The local effects of IL-6 include lymphocyte activation and maturation and increased antibody production, while the systemic effects of IL-6 include increased body temperature leading to fever, and induction of acute-phase proteins (Murphy &

Weaver, 2017). Interleukin-6 has both pro- and anti-inflammatory functions when secreted by other tissues. It is also known as one of the main myokines, or cytokines secreted by skeletal muscle, that plays an integral role in crosstalk between muscle with bone, liver, adipose, and other organs (Gomarasca et al., 2020; Pedersen & Febbraio, 2012; Petersen & Pedersen, 2005). Interleukin-6 can regulate bone resorption and formation, and stimulate metabolism through the promotion of glycogenolysis, gluconeogenesis, fatty acid oxidation, protein catabolism, glycerol release, and lipolysis (Gomarasca et al., 2020). When IL-6 is released from skeletal muscle and hepatic cells, it is more commonly associated with anti-inflammatory actions (Karsenty & Ferron, 2012; Karsenty & Mera, 2018; Pedersen & Febbraio, 2012). When IL-6 is secreted from adipose tissue, it tends to have a pro-inflammatory effect due to the ability of fatty acids to stimulate the release of IL-6 with other pro-inflammatory biomarkers including TNF-α, and monocyte-chemotactic proteins (He et al., 2018; Watanabe et al., 2004). These biomarkers activate pro-inflammatory signaling pathways such as janus kinase, a signal transducer and activator of transcription proteins, protein kinase B (PKB and/or AKT), and extracellular signal-regulated kinases (ERK), that when dysregulated from persistent IL-6 release, may result in cancer growth and CVD (He et al., 2018; Watanabe et al., 2004).

In clinical settings, IL-6 is measured to indicate the presence of activated and migrating macrophages and lymphocytes. Normal serum concentrations in healthy individuals without disease or chronic inflammation are usually ≤ 1.8 pg/mL (Libardi et al., 2012), and normal plasma concentrations are usually considered < 6.4 pg/mL in men and < 5.8 pg/mL in women (Fernandez-Real et al., 2001). In situations involving acute inflammation, serum IL-6 concentrations can become elevated. For example, serum IL-6 concentrations are as high as 64 pg/mL in those with acute respiratory syndrome coronavirus 2 (X. Chen et al., 2020). The

primary action of IL-6 is to control the intensity of inflammatory response; however, overproduction can lead to tissue damage. In chronic inflammatory states, concentrations of IL-6 can vary. For example, serum IL-6 concentrations can range between 0.9-3 pg/mL in those with obesity (Herder et al., 2007; Maachi et al., 2004), 30-494 pg/mL in those with autoimmune disorders (Ali et al., 2019), and 2.4-3.1 pg/mL in those with major depressive disorder (Karlović et al., 2012).

C-reactive protein is an important acute-phase protein that is synthesized in the liver during inflammation (Gabay & Kushner, 1999). Interleukin-6 is one of the main signals which stimulates the production of CRP. It is important to note that there are other regulatory inflammatory cytokines including IL-1β and TNF-α, and other acute-phase proteins involved in the systemic response to inflammation as well (Gabay & Kushner, 1999). C-reactive protein has several isoforms and is also synthesized in smooth muscle cells, macrophages, endothelial cells, lymphocytes, and adipocytes (Sproston & Ashworth, 2018). In the inflammatory process, the function of monomeric CRP is to respond to acute infection by binding to and/or coating the bacterium or fungal cell wall, a process known as opsonization. This action will, in turn, activate complement system proteins to ultimately generate a large phagocytic cell response at the site of infection (Murphy & Weaver, 2017). Increasing concentrations of monomeric CRP further activates leukocytes and increases the production of IL-6 as well as TNF-α, IL-1β, and IFN- γ (Gratacos et al., 1994; Schindler et al., 1990). As a result, the pro-inflammatory signaling pathways phosphatidylinositol-3-kinase (PI3K), AKT, and ERK are activated (Khreiss et al., 2002). C-reactive protein also has anti-inflammatory actions which are related to its cyclic, pentameric structure. This structure allows CRP to regulate apoptosis by affecting the cell cycle kinetics of monocytes (Kim et al., 2014). Pentameric CRP is also known to regulate PI3K/AKT

and ERK pathways which may lead to the inhibition of apoptosis, opsonization of apoptotic cells, and phagocytosis of damaged neutrophils (Khreiss et al., 2002).

In clinical settings, concentrations of CRP are monitored to measure infection, CVD risk, and other chronic inflammatory conditions. Normal concentrations of serum CRP in healthy individuals are usually around 0.8 mg/L and normal plasma concentrations are usually < 0.3 mg/L (Fernandez-Real et al., 2001; Libardi et al., 2012; Ridker, 2003). It is important to note that concentrations of serum and plasma CRP can vary. C-reactive protein concentrations can increase 1,000-fold in acute, bacterial infections (Thompson et al., 1999) and serum CRP can also increase to 89 mg/L in patients with acute viral infections such as acute respiratory syndrome coronavirus 2 (X. Chen et al., 2020). In more chronic conditions, serum CRP is around 6 mg/L in obese individuals, and ranges between 2.2-3.2 mg/L in those with major depressive disorder (Marzolini et al., 2020). It is also important to note that the definition of a healthy CRP concentration can vary depending on health status (Tsalik et al., 2012), thereby making it difficult to establish universal standards. For example, according to the CVD risk stratification system that uses CRP to predict the risk of CVD events, serum CRP concentrations < 1 mg/L are considered low risk, 1-3 mg/L are considered moderate risk, and > 3 mg/L are considered high risk (Lee et al., 2019; Ridker, 2003). On the other hand, the rheumatoid arthritis (RA) risk stratification system which measures CRP to gauge RA activity and subsequent RA episodes, considers serum CRP concentrations < 3.0 mg/L as normal, 3-10 mg/L as high risk, and > 10 mg/L as the RA diagnostic indicator (Sokka & Pincus, 2009).

Acute and Chronic Exercise and Inflammation

While exercise is defined as planned and structured activity such as aerobic exercise or resistance training, physical activity is a more general term and is defined as any activity that

involves caloric expenditure. Both exercise and physical activity influence inflammatory processes in the body. A single bout of exercise increases concentrations of IL-6 (Cipryan et al., 2015; Mendham et al., 2011). Though plasma IL-6 concentrations can increase as much as 100-fold in the bloodstream after intense exercise of either heavy volume or duration (Fischer, 2006; Gomarasca et al., 2020; Hardee et al., 2018), the increases are transient, and do not remain elevated in the blood stream (Cipryan et al., 2015; Fischer, 2006; Mendham et al., 2011). After a single bout of strenuous aerobic exercise, the plasma concentration of the inflammatory cytokines TNF-α and IL-1β increase along with IL-6, but cytokine inhibitors IL-1ra and soluble tumor necrosis factor receptors 1 and 2 are also secreted which help to control the inflammatory response (Ostrowski et al., 1999). Furthermore, when IL-6 is infused at concentrations similar to those observed during strenuous exercise (140 pg/mL), there is an increase in IL-10 and IL-1ra production. These cytokines are also known to mitigate TNF-α and IL-1β actions (Steensberg et al., 2003).

Chronic exercise training consisting of aerobic and resistance exercise reduces resting concentrations of IL-6 in a wide variety of special populations (Abd El-Kader & Al-Jiffri, 2019; Dieli-Conwright et al., 2018; Oberbach et al., 2008; Sardeli et al., 2018). In older adults with age-related, low-grade inflammation, higher frequency and longer duration of resistance training reduces resting concentrations of IL-6 (Sardeli et al., 2018). In elderly individuals, 6 months of aerobic exercise training significantly decreased IL-6 concentrations by 40% (Abd El-Kader & Al-Jiffri, 2019). Additionally, IL-6 concentrations are reduced after 9 weeks of exercise training in those with impaired glucose intolerance (Oberbach et al., 2008), and after a 16-week combined aerobic and resistance exercise intervention in cancer survivors (Dieli-Conwright et al., 2018). In healthy populations, some research showed that exercise training significantly

reduces resting IL-6 concentrations (Forti et al., 2017; Tesema et al., 2019), and other research did not (Stewart et al., 2007). This variation in response may be linked to the large range of resting IL-6 values observed in the healthy population, which often makes it difficult to detect statistically significant changes.

Acute exercise does not immediately affect serum CRP concentrations (Cipryan et al., 2015; Mendham et al., 2011). Though CRP concentrations increased to 0.68 mg/L and 0.84 mg/L after a 40-minute bout of moderate-vigorous intensity resistance exercise and moderate-vigorous intensity aerobic exercise, respectively, these values were not significantly different from basal values (Mendham et al., 2011). No differences from pre-exercise values were observed after a single bout of maximal exercise in 30 males (Cipryan et al., 2015), and after a 60-minute bout of treadmill walking at personalized speeds and 8% incline in hyperglycemic men and women (Nygaard et al., 2017). This lack of an acute exercise-induced CRP response is likely because IL-6 needs time to signal for CRP synthesis in hepatocytes, resulting in a longer period before CRP can enter the blood stream.

Chronic exercise decreases concentrations of CRP (Mattusch et al., 2000; Smith et al., 1999; Stewart et al., 2007). In individuals at risk for CVD, 6 months of an individualized exercise program reduced CRP concentrations from 5.3 mg/L to 4.4 mg/L (Smith et al., 1999), and in patients with hypertension and chronic kidney disease, 16 weeks of aerobic and resistance training reduced CRP by 85% (Barcellos et al., 2018). These effects are not limited to the diseased population. Average CRP concentrations were observed to decrease by 31% in healthy adults after 9 months of marathon training (Mattusch et al., 2000), and by 58% in both young and old adults after 12 weeks of aerobic and resistance training (Stewart et al., 2007). These studies support the notion that exercise training affects the inflammatory process which is reflected in

circulating concentrations of CRP. This action may be linked to the consistent, transient increases in IL-6 produced by exercise, which over time, may downregulate basal CRP production (Beavers et al., 2010).

Physical Activity and Inflammation

Regular physical activity, which is typically measured using daily step counts with an accelerometer, is also known to affect IL-6 and CRP concentrations (Kasapis & Thompson, 2005; Moy et al., 2014; Webb et al., 2018). These improvements have been noted in situations where step counts were increased or when individuals met a specific step count cut point. For example, in older adults with chronic obstructive pulmonary disease, adding 1000 steps/day resulted in a 39% decrease in CRP concentrations and a 32% decrease in IL-6 concentrations (Moy et al., 2014), and in women diagnosed with polycystic ovary syndrome, adding 1000 steps/day resulted in a 13% decrease in both IL-6 and CRP concentrations (Webb et al., 2018). These findings are similar in those with chronic kidney disease in which walking more than 10,000 steps/day for 3 months significantly reduced CRP and IL-6 concentrations compared to <5,000 and 5,000-9,999 steps per day (Zang et al., 2019). Obtaining 11,000 steps/day also resulted in a 21% decrease in CRP concentration in obese women (Renault et al., 2017). High levels of physical activity might also help reduce the potential for an exaggerated inflammatory response. For example, individuals who met a criterion of at least 12,500 steps per day for 14 days had a reduced IL-6 response to 14 days of high fructose meals (Bidwell et al., 2014). Additionally, cancer patients who experience treatment-related inflammation benefit from physical activity and exercise, suggesting that muscle-derived IL-6 from physical activity and exercise may be a mechanism to assuage the inflammatory response (Wood et al., 2009). Taken together, these studies suggest that increasing physical activity as measured through steps per

day or trying to meet a specific step count goal can reduce chronic inflammation as measured by both IL-6 and CRP.

Neuroinflammation and Brain Derived Neurotrophic Factor

Neuroinflammation, or inflammation of the brain and spinal cord, is mediated by local, resident immune cells in the brain, known as microglia (Lenz & Nelson, 2018). Microglia can produce cytokines and chemokines similar to M1 and M2 type macrophages, depending on the needs of the microglia (Lenz & Nelson, 2018). For example, microglia adopt the pro-inflammatory M1 phenotype and release IL-6, IL-1β, interferon gamma, and TNF-α in chronic neurological diseases. This transition is associated with reduced neuronal plasticity and cognitive impairment (Lenz & Nelson, 2018; C. H. Liu et al., 2017; Mosser & Edwards, 2008). Microglia will adopt the anti-inflammatory M2 phenotype and regulate cell proliferation and synaptic patterning by releasing factors such as IL-10 and IL-13 to remodel and repair tissue in early life development (Lenz & Nelson, 2018; Lobo-Silva et al., 2016). In exercise, microglia take on an anti-inflammatory role. In a model using aged mice, voluntary wheel running inhibited microglial activation by preventing microglia from adopting an M1 phenotype after a lipopolysaccharide (LPS) challenge which resulted in decreased neuronal degeneration (Littlefield et al., 2015). In a murine model of Parkinson's Disease, structured treadmill running alleviated dopaminergic neuronal loss by inhibiting microglial activation (Sung et al., 2012). Activation was inhibited through the reduction of cell surface marker CD11b expression on microglial cells in the striatum (Sung et al., 2012).

Microglia can also synthesize and release brain-derived neurotrophic factor (BDNF), a critical protein for the maintenance of neuronal health (Brigadski & Leßmann, 2020; Gomes et al., 2013). Brain-derived neurotrophic factor is synthesized as pro-BDNF, which is involved with

pathways leading to cell death and apoptosis (pruning mechanisms), or mature-BDNF, which results in intracellular phosphorylation, triggering cell survival and differentiation pathways (Thomas & Davies, 2005). In a study evaluating the ability of inflammation to control pro- and mature-BDNF release from microglia in a N9 murine microglial cell line, 6 hours of LPS stimulation resulted in no changes in pro-BDNF production and a significant decrease in mature-BDNF production compared with non-LPS stimulated cells (Gomes et al., 2013). This suggests that prolonged inflammation is deleterious to microglial survival and differentiation. Interestingly, overexpression of BDNF from microglia affects BDNF receptor tropomyosin receptor kinase B (TrkB), resulting in downstream molecular dysregulation and disease (Ding et al., 2020; Radin & Patel, 2017). For example, a murine microglial model of cystitis showed that 17 days of i.p. injections of inflammatory cyclophosphamide significantly increased microglial release of BDNF which subsequently increased concentrations of IL-1β and TNF-α (Ding et al., 2020). When BDNF and tropomyosin receptor kinase B (TrkB) signaling was blocked using a TrkB receptor antagonist, microglial activation was reduced; however, when an intrathecal injection of exogenous BDNF was given, BDNF further promoted the activation of microglia and increased release of IL-1β and TNF-α (Ding et al., 2020).

Brain-derived neurotrophic factor can cross the blood brain barrier (Pan et al., 1998), act via autocrine and paracrine mechanisms, and bind to cells with TrkB receptors such as muscle, liver, heart, immune, and hematopoietic cells (Pan et al., 1998). It is important to note that other cells beyond the CNS can also produce and store BDNF. Clinical research confirms that activated T and B cells (Kerschensteiner et al., 1999), hematopoietic cells (Fujimura et al., 2002; Urabe et al., 2013), and skeletal muscle fibers (Matthews et al., 2009) can produce BDNF, and approximately 90% or more of peripheral BDNF is stored in platelets (Fujimura et al., 2002).

Studies show that platelets activated by traumatic injury assist in local repair by releasing BDNF to bind cells with the TrkB receptor (Fujimura et al., 2002), and skeletal muscles produce BDNF during muscular contractions to regulate energy homeostasis (Matthews et al., 2009; Yamamoto & Gurney, 1990). Human skeletal muscle BDNF regulates fatty acid metabolism through increases in the phosphorylation of AMP-activated protein kinase within the myocyte (Matthews et al., 2009), suggesting that muscle-derived BDNF functions as a myokine. Overall, BDNF can be synthesized in both central and peripheral tissues and has local and global effects on many target cells that play a role in inflammation and energy balance.

Acute and Chronic Exercise, and Brain-Derived Neurotrophic Factor

Acute and chronic exercise mitigate neuroinflammation and research suggests that BDNF may play a role in positive exercise-related responses in patients with neurological diseases. Clinical trials show that an acute bout of 10-30 minutes of moderate exercise significantly and transiently increased basal serum BDNF concentrations in individuals with progressive multiple sclerosis (MS; Briken et al., 2016; Gold et al., 2003). In healthy individuals, acute exercise also transiently increased concentrations of BDNF. These studies have utilized a 20-minute bout of treadmill exercise (Boyne et al., 2019), a 30-minute bout of moderate-intensity walking break between periods of long sitting (Wheeler, Green, et al., 2020), and a 20-minute bout of intense cycling (Skriver et al., 2014). After acute exercise, BDNF concentrations return to baseline levels or lower (Briken et al., 2016; Cabral-Santos et al., 2016; Castellano & White, 2008). It has been proposed that peripheral BDNF clearance reflects movement into the CNS for neuronal processing (Castellano & White, 2008) and movement into the muscle to assist in lipid oxidation (Rasmussen et al., 2009).

Chronic exercise training seems to have the same positive effect in patients with neurological disease. Serum BDNF concentrations significantly increased in patients with Parkinson's Disease after 7 days of motor rehabilitation training (Angelucci et al., 2008), 28 days of aerobic exercise (Frazzitta et al., 2014), 12 weeks of high intensity interval training (HIT) (O'Callaghan et al., 2020), and 8 weeks of structured cycling (Zoladz et al., 2014). However, the effect of exercise training on BDNF concentrations in other neurological disease populations and in healthy individuals is conflicting. One randomized, controlled trial found that 24 weeks of aerobic and resistance training in patients with multiple sclerosis significantly increased BDNF compared with baseline and sedentary controls (Wens et al., 2016). This finding contrasts with another study that found that 9 weeks of endurance training did not change resting BDNF concentrations in patients diagnosed with multiple sclerosis (Briken et al., 2016). In healthy individuals, one study found that chronic exercise training and BDNF are strongly and positively correlated (De la Rosa et al., 2019), and that a few weeks to one year of chronic exercise training increases basal BDNF concentrations (Erickson et al., 2011; Nofuji et al., 2008). However, other studies show that habitual exercise has no effect on BDNF concentrations in healthy individuals (Schiffer et al., 2009).

Relationship Among Biomarkers Brain-Derived Neurotrophic Factor, Interleukin-6, and C-Reactive Protein

Animal and human research shows that changes in BDNF are associated with changes in IL-6 and CRP. Several studies exploring the underpinnings of depression revealed an inverse relationship between BDNF and IL-6 and CRP concentrations. Two weeks of stress-induced depression in rats resulted in significant increases in plasma IL-6 and CRP concentrations and these increases were significantly and negatively correlated with BDNF protein expression in the

hippocampus (Han et al., 2018). This same IL-6, CRP and BDNF relationship has been observed in humans. When perimenopausal women were divided into those with and without depression, the depressed group had significantly higher concentrations of IL-6 and CRP, and significantly lower concentrations of serum BDNF when compared to the non-depressed group (Guo et al., 2018).

This inverse relationship between inflammatory proteins and BDNF also seems present in exercise studies. Clinical studies show that exercise interventions simultaneously reduce IL-6 and CRP, and increase BDNF concentrations in those with cancer (Zimmer et al., 2018), MS (Briken et al., 2016), mild cognitive impairment (Tsai et al., 2019), and Parkinson's Disease (Landers et al., 2019). However, some studies show that long-term exercise in healthy individuals results in decreased BDNF concentrations with no associated changes in IL-6 concentrations (Wagner et al., 2015). One study found that BDNF concentrations decreased in young, healthy males after 6 weeks of aerobic exercise, and there were no noteworthy changes or relationships with respect to IL-6 concentrations (Wagner et al., 2015). This lack of relationship suggests that there may be unknown BDNF processing mechanisms during exercise that may be affected by the increase in IL-6 concentrations observed during acute exercise.

Although both BDNF and IL-6 are involved in energy homeostasis during exercise, the relationship among BDNF, IL-6, and CRP during exercise has yet to be fully elucidated. Like BDNF, muscle-derived IL-6 regulates fatty acid metabolism through AMP-activated protein kinase signaling during exercise (Matthews et al., 2009; Pedersen & Febbraio, 2012). High volume high intensity training results in increased BDNF and IL-6 concentrations compared to resting values in healthy men (Cabral-Santos et al., 2016). In this study, no significant interactions were found between BDNF and IL-6 although a significant interaction was found

between IL-6 and IL-10 (Cabral-Santos et al., 2016). Many other exercise studies with healthy individuals demonstrate this transient increase and further support the potential for anti-inflammatory actions of both proteins (Boyne et al., 2019; Fischer, 2006; Gomarasca et al., 2020; Hardee et al., 2018; Skriver et al., 2014; Stewart et al., 2007; Wheeler, Green, et al., 2020). However, more information related to the mechanisms of exercise-induced reductions in BDNF is needed.

Cannabidiol

Cannabidiol (CBD) is a phytocannabinoid derived from the plant *Cannabis sativa L*. There are more than 400 phytocannabinoids; and trans-delta9-tetrahydrocannabinol (THC) and CBD are the most well-studied (Gaoni & Mechoulam, 1964). These cannabinoids are biosynthesized, converted into acids, then decarboxylated into their THC and CBD forms (Bonini et al., 2018). The biosynthesis of THC and CBD begins with geranyl diphosphate and olivetolic acid which are converted into cannabigerolic acid, the common precursor for tetrahydrocannabonolic acid and cannabidiolic acid (Bonini et al., 2018). Although tetrahydrocannabonolic acid and cannabidiolic acid have the same molecular composition, decarboxylation results in structural changes to the molecule, resulting in a tri-cyclic structure in THC and a bi-cyclic structure in CBD (Bonini et al., 2018).

Regular use of THC is associated with psychosis and may increase the risk of developing a psychotic illness later in life (Marconi et al., 2016; Moore et al., 2007). The 1970 Controlled Substances Act signed by President Nixon established cannabis as a Schedule I drug, conferring that there was no medical use for cannabis and that the compound had a high potential for abuse (Spillane & McAllister, 2003). Almost 50 years later in June 2018, overwhelming support for the use of CBD for treatment-resistant seizures (Devinsky et al., 2014, 2017, 2018) led to FDA

approval of pharmaceutical grade CBD for the treatment of rare epilepsy disorders. Six months later, hemp-derived cannabis, including CBD and its derivatives with less than 0.3% THC, were removed from the definition of marijuana in the Controlled Substance Act. These policy changes have led to renewed efforts to use CBD in a variety of clinical settings.

The function of CBD was first observed through its interactions with receptors of the ECS (Matsuda et al., 1990; Munro et al., 1993). The ECS is a conserved biological system consisting of endocannabinoids AEA and 2-AG, and their G protein-coupled receptors of the G_0 and G_i type, known as CB1r and CB2r. Anandamide and 2-AG are degraded by fatty acid amide hydrolase (FAAH) and monoacylglycerol lipase (MAGL), respectively (Di Marzo & De Petrocellis, 2012; Sugiura et al., 2002).

Cannabinoid receptor location and concentration are reported to be species-dependent (Q. R. Liu et al., 2009; Zhang et al., 2014). Animal models demonstrate high levels of CB1r expression in the brain, peripheral neurons, and glia (Ativie et al., 2018; Chiarlone et al., 2014; Navarrete et al., 2020), as well as in the reproductive and endocrine organs (Navarrete et al., 2020; Walker et al., 2019). Although CB2r was initially thought to exist primarily in the spleen and immune system (Turcotte et al., 2016), it is also expressed in the brain in a species dependent manner (Q. R. Liu et al., 2009; Stempel et al., 2016; Zhang et al., 2015, 2014). Humans have two isoforms, cannabidiol receptor 2a (CB2ra), which is mainly expressed in the testis and brain, and cannabidiol receptor 2b (CB2rb), which is expressed in the spleen and leukocytes (Q. R. Liu et al., 2009). Both receptors activate numerous signaling pathways including PI3K and mitogen-activated protein kinase, regulate cytosolic calcium via phospholipase C, and act to inhibit other enzymes such as adenylyl cyclase (Luchicchi & Pistis, 2012; Munro et al., 1993; Pertwee, 1997; Turcotte et al., 2016). The regulation of these pathways

is the proposed mechanism used by the ECS to maintain homeostasis and is also proposed as potential therapeutic targets for the treatment of pain, inflammation, obesity, anxiety, and fear (Calignano et al., 1998; Di Marzo, 2018; Fine & Rosenfeld, 2013; Ligresti et al., 2016; Ruehle et al., 2012; Schulz et al., 2021).

Cannabidiol and Inflammation

The effect of CBD on IL-6 production in inflammatory responses is thought to involve interaction with ECS and non-ECS receptors (Couch et al., 2017; Muthumalage & Rahman, 2019; Petrosino et al., 2018). Cannabidiol is recognized as a negative allosteric modulator of human CB1r (Laprairie et al., 2015; Tham et al., 2019), a partial agonist of CB2r (Tham et al., 2019), and an enhancer of endogenous AEA signaling by inhibiting AEA endocytosis along with CB1r and CB2r and its breakdown via FAAH (Bisogno et al., 2001; Petrosino et al., 2018). In human keratinocytes stimulated with 100 μg/mL of polyinosinic:polycytidylic acid (poly I:C) for 6, 12, and 24 hours, cells treated with CBD at 1, 5, 10, and 20 μM significantly inhibited the release of IL-6, TNF-α, and monocyte chemotactic protein 2 at the 6-hour time point compared to the control group (methanol) in a dose-dependent manner (Petrosino et al., 2018). The same study also found that the highest doses of CBD (10 and 20 μM) significantly reduced the largest increases in IL-6 and TNF-α at the 12- and 24-hour time points. Additionally, the study explored the mechanisms of CBD-induced reductions in inflammation. Cannabidiol acted through CB2r and transient receptor potential vanilloid type-1, and increased AEA concentration which subsequently reduced monocyte-chemotactic proteins 2 and IL-6 levels secreted from treated cells (Petrosino et al., 2018). In a separate *ex vivo* model, 10 μM of CBD inhibited cytokine production and inflammatory pathways after treatment with 10 ng/mL of interferon gamma for 8 hours followed by 10 ng/mL of TNF-α for 16 hours in tissue explants taken from patients with

bowel cancer, inflammatory bowel disease, and emergency appendectomy (Couch et al., 2017). These results suggest that in inflammatory conditions, CBD suppresses the pro-inflammatory cascade in enteric glial cells. Enteric glial cells are similar to microglia in that they mediate inflammatory responses in the enteric nervous system of the gut (Couch et al., 2017). A second component of this same study found that the inhibition of inflammation is mediated by the interaction of CBD with receptors CB2r, transient receptor potential vanilloid type-1, peroxisome proliferator-activated receptor alpha and gamma, and G protein-coupled receptor 55 (Couch et al., 2017). Given these responses, it appears that the effect of CBD on inflammation may involve multimodal relationships among many cellular pathways.

Research suggests that CBD has simultaneous pro- and anti-inflammatory actions in various inflammatory conditions. Intranasal lipopolysaccharide (LPS; 10 μg) administration followed by 3 days of CBD treatment (75 mg/kg) in mice significantly increased the number of neutrophils at the 6 and 24-hour time points, and the number of monocytes at the 24-hour time point, showing that CBD enhances immune cell migration and LPS-induced pulmonary inflammation (Karmaus et al., 2013). The same study found no effect of CBD on LPS-induced TNF-α and IL-6 mRNA expression in lung tissue; however, CBD significantly enhanced TNF-α, IL-6, and granulocyte colony stimulating factor mRNA expression at the 24-hour post-LPS time point. Other murine models of acute lung injury and function show opposing results with CBD treatment (Ribeiro et al., 2015, 2012). After LPS was administered intranasally at 100 μg/mL, treatment with 10, 20, 30 and 80 mg/kg of i.p. CBD produced anti-inflammatory effects in lung tissue in a dose-dependent manner (Ribeiro et al., 2012). More specifically, 20, 30, and 80 mg/kg of i.p. CBD decreased leukocyte migration into the lungs 1 day after LPS induction, 10, 20, 30, and 80 mg/kg of i.p. CBD decreased TNF-α production in the bronchoalveolar lavage fluid 1 day

after LPS induction, and 20 mg/kg of i.p. CBD decreased neutrophil, lymphocyte, and macrophage migration into the lungs at 1, 2, and 4 days after LPS induction (Ribeiro et al., 2012). In a follow-up study by the same authors, 20 and 80 mg/kg of CBD significantly decreased LPS-induced TNF-α and IL-6 concentrations in lung tissue, reduced lung airway resistance, and also increased lung elastance in a dose-dependent manner (Ribeiro et al., 2015).

In human cells, CBD also has both pro- and anti-inflammatory effects. Human monocytes from pleural tissue stimulated with LPS showed that 10.6 μM of CBD treatment significantly reduced their production of C-C motif chemokine ligands 2 and 5, chemoattractants involved with inflammation processes that act through transmembrane G-coupled receptors to signal for migration of immune cells (Muthumalage & Rahman, 2019). The same study found that CBD treatment reduced nuclear factor kappa B (NF-κB) transcription factor activity and interleukin-8 (IL-8) concentrations in the LPS stimulated human bronchial epithelial cells and lung fibroblasts. Additionally, the same study also observed that exposure to CBD aerosols without LPS stimulation significantly elevated concentrations of IL-1ra and IL-8 from the monocytes, IL-8 from the bronchial epithelial cells, and IL-6 and IL-8 from lung fibroblasts compared to untreated cells. Taken together, these findings suggest that although CBD has an anti-inflammatory effect by mitigating LPS-induced cytokines, CBD may also enhance pro-inflammatory cytokines.

Other research suggests that CBD may not influence overall measures of systemic inflammation. A rodent study investigating the effect of 5 mg/kg of i.p. CBD on induced myocardial ischemia found that CBD-treated mice experienced a decrease in serum IL-6 concentrations, but no differences in serum CRP and TNF-α concentrations compared to controls (Durst et al., 2007). In this study, researchers demonstrated that CBD treatment 1 hour before

ischemia and daily for 7 days before sacrifice had *in vivo* cardioprotective effects associated with reduced IL-6 concentrations, but no other systemic cytokines were changed (Durst et al., 2007). Human research suggests that CBD has no effect on systemic inflammatory markers. One study showed that after 8 weeks of 20 mg of sublingual CBD oil per day, CRP concentrations in individuals with Crohn's Disease were unchanged (Naftali et al., 2017) and 13 weeks of 200 mg of daily oral CBD failed to change concentrations of CRP, TNF-α, and IL-6 in subjects with type 2 diabetes and dyslipidemia (Jadoon et al., 2016). It is important to note the difficulty in comparing all CBD studies due to differences in CBD dosages, administration routes, durations of CBD administration, as well as the models used to test the compound. In general, rodent models utilize intranasal application or i.p. CBD injections ranging from 1 mg/kg/day to 10 mg/kg/day (Barichello et al., 2012; Durst et al., 2007; Esposito et al., 2011; Mori et al., 2017), and human neurological research uses oral CBD solutions ranging from 50 mg/day to 800 mg/day, depending on the age range and disease type (Carlini & Cunha, 1981; Consroe et al., 1986; Leweke et al., 2012).

The Influence of Cannabidiol on Exercise and Physical Activity

Research evaluating the effects of CBD in response to acute and chronic exercise is currently nonexistent in humans and scarce in animals (Langer et al., 2021). Only one recent study evaluated the effects of a single dose of CBD (100 mg/kg) 18 hours following an acute bout of eccentric hindlimb loading in rodents (Langer et al., 2021). When the tibialis anterior muscle and liver tissues were analyzed, no differences in downstream targets of mechanistic target of rapamycin 1were found between CBD-treated rats and controls; however, phosphorylation of NF-κB was significantly lower in CBD-treated rats (Langer et al., 2021). This suggests that CBD may have no effect on anabolic or catabolic muscle functions. However,

phosphorylation of NF-κB was higher in the liver of the CBD-treated rats compared to controls (Langer et al., 2021), suggesting that CBD may be acting in a tissue-dependent manner during exercise. It is unknown as to whether CBD affects molecular signaling in skeletal muscle during chronic aerobic and/or resistance training, and if any effect is similar in all skeletal muscle fiber types.

Despite anecdotal claims made by both recreational and elite athletes, there is no convincing evidence supporting the use of CBD for performance enhancement. More specifically, the popular medical belief is that CBD has anti-inflammatory, analgesic, and anxiolytic effects, neuroprotective benefits, and helps with sleep disturbances, but these speculations are only substantiated by results from preclinical studies (McCartney et al., 2020). There is some literature exploring the effects of cannabis on cardiovascular measures, pulmonary function, grip strength, work capacity, and metabolic rate in healthy individuals (Lisano et al., 2020, 2019; Renaud & Cormier, 1986; Steadward & Singh, 1975), but these studies do not separate CBD from cannabis and do not include an exercise component. Additionally, some suggest that cannabis use may help with chronic pain and exercise recovery, but more human studies with both a cannabis use group and a CBD-only group are necessary (Gillman et al., 2015; Kennedy, 2017; Ware et al., 2018).

There was scant human research exploring the effects of CBD on measures of physical activity including total exercise time and steps per day. One survey on cannabis use before and after exercise found that 70% of 605 respondents prefer to use cannabis before working out to make exercise feel more enjoyable, 79% strongly agreed cannabis enhances recovery, and 52% strongly agreed that cannabis increased their motivation to exercise (YorkWilliams et al., 2019). Interestingly, bivariate analyses revealed respondents who used cannabis with exercise were

younger, male, and had lower BMI than those who did not use cannabis with exercise (YorkWilliams et al., 2019). This survey agrees with others that found that athletes use CBD for perceived pain and recovery benefits (Kasper et al., 2020; Zeiger et al., 2019). These findings suggest that perhaps a mixture of CBD and THC induces endorphins, activates opioid receptors, and alters physical activity behavior; however, very little research has explored these mechanisms. When cannabis was used in a mouse model to explore wheel-running preference and running motivation, THC had no effect on exercise motivation (Hurel et al., 2021). There are no studies using CBD in this model. Consequently, when it comes to the effect of CBD on physical activity behavior, no conclusive evidence exists.

Cannabidiol and Brain-Derived Neurotrophic Factor

Much of the evidence exploring the effects of CBD on BDNF has originated in animal studies aimed at exploring the potential of CBD to provide neuroprotective effects in neurodegenerative conditions (Barichello et al., 2012; Esposito et al., 2011; Mori et al., 2017). In a murine model of transient cerebral ischemia, in which carotid arteries were occluded with clamps for 20 minutes, i.p. CBD (10 mg/kg) 30 minutes before and 3, 24, and 48 hours after ischemia significantly decreased hippocampal neurodegeneration, which was verified by lowered expression of apoptotic factors including caspase-9 proteins in hippocampal tissue (Mori et al., 2017). Additionally, these same CBD-treated mice experienced decreased hippocampal neuroinflammation and only the CBD-treated mice increased hippocampal BDNF concentrations compared to the sham and vehicle groups (Mori et al., 2017). In another compelling study, CBD attenuated neuroinflammation through interaction with the transcription factor peroxisome proliferator-activated receptor gamma in both an *in vitro* rodent model of cultured astrocytes and an *in vivo* rodent model of Alzheimer's Disease (Esposito et al., 2011). More specifically,

astrocytes treated with pathological amyloid beta peptides $A\beta_{1-42}$ for 24 hours increased production of IL-1β and TNF-α, but treatment with CBD significantly attenuated cytokine production in a dose-dependent manner through peroxisome proliferator-activated receptor alpha and gamma activation and inhibition of NF-κB (Esposito et al., 2011). Hippocampal tissue collected from amyloid beta peptides $A\beta_{1-42}$ injected rats showed that 15 days of i.p. CBD (10 mg/kg) inhibited microglial reactivity, maintained neuronal integrity of the CA1 region of the hippocampus, and stimulated basal neurogenesis compared to the control group (Esposito et al., 2011). Though BDNF concentrations were not directly measured in this study, the hippocampal CA1 region is usually included in models of brain plasticity where BDNF/TrkB is observed to increase neuronal density during periods of growth or cellular survival (Alonso et al., 2004).

The duration of CBD treatment may also play a significant role in the ability of the compound to alter BDNF. For example, a single dose of i.p. CBD (2.5, 5, and 10 mg/kg) differed from extended treatments of CBD (2.5, 5, and 10 mg/kg for 9 days) with respect to TNF-α, IL-1β, IL-6, and BDNF concentrations in rats subjected to pneumococcal meningitis (Barichello et al., 2012). Acute treatment of i.p. CBD (2.5, 5, and 10 mg/kg) to rats 6-hours post meningitis induction showed no significant reduction in TNF-α, IL-1β, and IL-6 response, nor stimulation of BDNF in the hippocampus and frontal cortex (Barichello et al., 2012). However, extended treatment reduced TNF-α and increased BDNF concentrations in the frontal cortex, but not in the hippocampus (Barichello et al., 2012). These results demonstrate that chronic administration of CBD has the potential to decrease inflammation and increase neuroplasticity in the areas most affected by the neuroinflammatory disease; however, these responses are time- and dose-dependent. Therefore, there is support for the use of CBD as a medical treatment, but significantly more evidence related to these issues is necessary.

Sex Differences

Biological sex is an important factor in structural, cellular, and molecular functions that affect overall health. These differences are linked to sex chromosomes and sex hormones. Generally, females have two X chromosomes and males have one X chromosome and one Y chromosome. In mammalian gonadal development, these sex chromosomes cause differentiation of sex organs. For example, the *Sry* gene, which is involved in making sex-determining region Y protein, is only located on the Y chromosome and the protein produced from this gene acts as a transcription factor in gonadal primordia to develop testes and prevent uterus and fallopian tube formation in males (Eggers et al., 2014). The differentiation of the testes establishes further developmental processes including gonadal hormone production of testosterone, estradiol, and progesterone (Eggers et al., 2014). The sex hormones estrogen and testosterone have permanent effects on body development such as in the development of the genitals or the brain. Other actions of these hormones are more temporary and depend on how long testosterone, estradiol, or progesterone are present (McEwen & Milner, 2017). Both sex chromosomes and sex hormones act on other organs and tissues and give rise to crucial differences in the structure and function of bodily systems. For example, the XX chromosome has regional effects on the brain that are independent of sex hormones, specifically in the growth and formation of the amygdala, hippocampus, and prefrontal cortex (Lentini et al., 2013). Additionally, higher levels of testosterone during brain development increase white-matter volume (Perrin et al., 2008).

Sex differences are present in the ECS. In the rodent amygdala, males have greater concentrations of AEA and 2-AG, and females have greater concentrations of the enzymes FAAH and MAGL (Krebs-Kraft et al., 2010). The endocannabinoids present in female rodents also have lower binding affinity for CB1r in the hypothalamus and enhanced binding affinity to

CB1r in the amygdala compared to males (C. J. N. Riebe et al., 2010). Research suggests that estrogen interacts with the components of the ECS. Estrogen administration affecting FAAH concentrations may lead to alterations in regulation of pain, inflammation, obesity, anxiety, and fear (Calignano et al., 1998; Di Marzo, 2018; Fine & Rosenfeld, 2013; Ligresti et al., 2016; Ruehle et al., 2012; Schulz et al., 2021). The interaction between estrogen and the ECS may provide a mechanism for sex-related disparities observed in metabolism and pain perception reported in men and women (Mogil, 2012; Paller et al., 2009).

Sex Differences in Inflammation

Although there are many potential sex differences with respect to the inflammatory process, the IL-6 response is one of the most explored. In resting conditions, average IL-6 concentrations are not significantly different between males and females (Edwards et al., 2006; Lockwood et al., 2016; Prather et al., 2009; Steptoe et al., 2002). However, there are sex differences in the IL-6 response to injury and stress. For example, male patients with acute injuries had 122% and 70% higher concentrations of systemic IL-6 concentrations after one day and two-days post trauma, respectively, compared to females (Mörs et al., 2016). Conversely, after an acute mental stress test, females had higher IL-6 concentrations compared to males, independent of age, BMI, and smoking status (Hackett et al., 2012). This study agrees with others supporting a more drastic and longer duration IL-6 response in females after stress-induced situations when compared to males (Edwards et al., 2006; Lockwood et al., 2016; Prather et al., 2009; Steptoe et al., 2002).

Sex differences with respect to CRP concentrations are most attributed to differences in adiposity and BMI (Khera et al., 2009; Rexrode et al., 2003; Thorand et al., 2006). Adipose tissue is a secretory organ known to contribute to low-grade systemic inflammation (Pedersen &

Febbraio, 2012). Women generally tend to have greater body fat percentage and fat mass when compared to men (Lovejoy et al., 2009; Thorand et al., 2006). In individuals (*n* = 1,413 males; n=1,166 females) ages 30-65 years old participating in the Dallas Heart study, average resting CRP concentrations for women and men were 3.6 mg/L and 1.9 mg/L, respectively, and CRP values were positively correlated to total fat mass in women (Khera et al., 2009). Interestingly, BMI and body fat percentage are significantly correlated with CRP concentrations in women, and BMI and waist to hip ratio are significantly and positively correlated to CRP concentrations in men (Thorand et al., 2006). However, stress-induced inflammatory responses may result in sex-related differences in CRP concentrations that are independent of body composition (Lockwood et al., 2016). For instance, after an acute mental stress test, IL-6 responses were positively correlated with high CRP concentrations in males, and IL-6 responses were negatively correlated with CRP concentrations in females (Lockwood et al., 2016). This suggests that CRP may be an indicator of current inflammatory status and the relationship between acute and chronic inflammation may be related to biological sex.

Sex Differences in Brain-Derived Neurotrophic Factor

Biological sex is also a major determinant of cortical and serum BDNF concentrations (Bus et al., 2011). Both clinical and preclinical studies suggest that the highest concentrations of BDNF are found in the neurons of the hippocampus, amygdala, cerebellum, and cerebral cortex (Hofer et al., 1990; Timmusk et al., 1993). Structural magnetic resonance imaging (MRI) studies demonstrate sex-related differences in both volume and tissue density of the amygdala and hippocampus (Kaczkurkin et al., 2019). These areas are implicated in emotional processing and cognitive function and have high concentrations of cannabinoid receptors (Ativie et al., 2018; Chiarlone et al., 2014; Navarrete et al., 2020). It is possible that BDNF concentrations may differ

in each brain structure according to sex, and that these differences may affect emotion and cognition. This regional difference hypothesis is clinically supported by sex-related disparities in the occurrence and diagnoses of neuropsychiatric disorders. Females are 1.5-2 times more likely to experience mood and anxiety disorders (McLean et al., 2011), and males are 4 times more likely to be diagnosed with schizophrenia and autism (Lenz & McCarthy, 2015). Low concentrations of BDNF are observed in patients with major depressive disorder and schizophrenia (Kang et al., 2015; Lang et al., 2004; Shoval & Weizman, 2005; Szuhany & Otto, 2020) which suggests BDNF may have a crucial role in mood and anxiety disorders.

Literature demonstrates that estrogen and testosterone affect brain structure and function and interact with BDNF in the CNS (Lentini et al., 2013; Lenz & Nelson, 2018; McEwen & Milner, 2017; Scharfman & MacLusky, 2006; Sohrabji & Lewis, 2006). Animal research on the effect of estrogen on neurons, glial cells, and hippocampal tissue shows that both estrogen and BDNF share common cellular targets and signaling pathways (Scharfman & MacLusky, 2006; Toran-Allerand, 2004; Warren et al., 1995). These cellular targets are located in the cerebral cortex, basal forebrain, hippocampus, and striatum, and involve the mitogen-activated protein kinase, PI3K, and phospholipase C pathways (Scharfman & MacLusky, 2006; Toran-Allerand, 2004; Warren et al., 1995). One study showed that when exogenous estrogen (10 μg of 17β-estradiol) was administered for 2 weeks to ovariectomized female rodents after artery occlusion to induce stroke-like symptoms, estrogen treatment resulted in increased hippocampal BDNF protein expression and reductions in depression-like symptoms (Su et al., 2016). In ovariectomized, young and middle-aged, female mice, estrogen (5 μg of 17β-estradiol) dorsally infused into the hippocampus decreased levels of histone deacetylases, increased BDNF protein, and increased the acetylation of BDNF gene promotors (Fortress et al., 2014). These results

suggest that estrogen has epigenetic effects on BDNF production. However, increased concentrations of estrogen can also affect BDNF regulation of synaptic transmission resulting in altered nerve terminal excitability which may increase seizure risk (Scharfman et al., 1999).

Testosterone is reported to have similar effects on neurogenesis, BDNF concentrations, and interactions with BDNF. For example, testosterone (2 mg/kg/day) treatment for 10 days after cerebral ischemia in castrated male rats increased serum and brain tissue (striatum, cortex and subventricular zone) BDNF concentrations (Fanaei et al., 2014; Yang & Arnold, 2000), and testosterone and BDNF (75 µL) treatment after axotomy in castrated male rats restored androgen receptor expression (Yang & Arnold, 2000). These studies suggest that BDNF and testosterone are interdependent. Overall, estrogen and testosterone contribute to sexual dimorphism in specific brain structures and interact with BDNF which suggests males and females experience differences in information processing, memory, cognitive function, emotion and mood, and behavior.

There is also evidence that stress may mediate an interaction between BDNF and inflammatory cytokines in a sex-dependent manner. For instance, an animal model of depression (exposure to 4 weeks of chronic, unpredictable mild stress) revealed sex-related differences in neuroinflammatory response (L. L. Liu et al., 2019). More specifically, female mice experienced a significant decrease in hippocampal BDNF mRNA expression and a significant increase in TNF-α mRNA expression compared to males. This decrease in BDNF was also positively corelated with depressive-like behaviors. Although both sexes experienced no differences in IL-6 mRNA expression, there was a significant interaction between stress and biological sex on IL-6, indicating that female mice were more sensitive to stress than males (L. L. Liu et al., 2019). Along these same lines, BDNF-knockout females were more sensitive to anxiety and depression-

like behavior after 52 days of mild stress when compared to wild type females (Autry et al., 2009). In the same study, no significant difference in behavior was observed between BDNF-knockout males and wild type males. Interestingly, this study also found that stress did not further reduce hippocampal BDNF concentrations in knockout mice (Autry et al., 2009), suggesting that some reduction in BDNF affects depression-related behaviors in females more than males.

In humans, the relationship between BDNF concentrations and biomarkers of inflammation is unclear. Resting, serum BDNF and inflammatory biomarker concentrations are reported to be similar in men and women in good health (Lang et al., 2004; Ziegenhorn et al., 2007). In patients with MS, biological sex does not contribute to differences in serum BDNF, IL-6, or TNF-α concentrations compared with healthy controls (Patanella et al., 2010). However, in adolescents with bipolar disorder, females had 8% higher BDNF and 44% higher CRP concentrations compared to males, and no sex-related differences in IL-6 concentrations (Goldstein et al., 2011). Taken together, animal and human research suggests that, in times of chronic stress, females experience declines in BDNF, which may in turn, translate to a greater vulnerability to higher inflammation, depression, and anxiety-related behaviors than males.

Sex Differences in Response to Exercise

Sex differences in the inflammatory response following acute and chronic exercise have been demonstrated in animal and human models. Mouse models of eccentric exercise show that females have less myofiber swelling, necrosis, and structural protein disruption compared with males (Komulainen et al., 1999) and less monocyte, macrophage, and neutrophil invasion into myofibers than males (St. Pierre Schneider et al., 1999). Sex-related differences in the inflammatory response and degree of muscle damage are also observed in humans. For example,

women had less leukocyte invasion into vastus lateralis myofibers compared to men after 3 sets of eccentric unilateral leg press and extension exercises performed at 120% of concentric one repetition maximum, and men had significantly higher plasma granulocyte counts and B-cell lymphoma positive inflammatory cells than women at the 48-hour time point (Stupka et al., 2000). In a separate study, young girls experienced significant increases in leukocyte and lymphocyte invasion, as well as increases in IL-6 concentrations after 60 minutes of cycling at 70% maximal oxygen uptake ($\dot{V}O_2$ max) compared to young boys of the same age (Timmons, Tarnopolsky, et al., 2006).

Research suggests that menstrual phase and contraceptive use may alter the female response to exercise. One study showed that women in the follicular and luteal phases taking oral contraceptives experienced fluctuations in leukocytes, neutrophils, and monocyte invasion after prolonged cycling and had 80% greater concentrations of IL-6 compared to women in the follicular phase without oral contraceptives (Timmons, Hamadeh, et al., 2005). In a similar study evaluating the influence of sex, age, and puberty on lymphocytes after 60 minutes of acute cycling, lymphocyte counts were greater in older men and women compared to younger boys and girls and 35% higher in prepubertal girls compared to prepubertal boys (Timmons, Tarnopolsky, et al., 2006).

In contrast, several studies suggest that the inflammatory response to chronic exercise and training is similar in men and women (Abd El-Kader & Al-Jiffri, 2019; Abd El-Kader & Al-Shreef, 2018; Beavers et al., 2010). After 12 months of moderate intensity exercise, IL-6, IL-8, and tumor necrosis factor receptor 1 concentrations were significantly decreased compared to a non-exercise control group and no differences were observed between men and women (Beavers et al., 2010). Although CRP concentrations had decreased at the 12-month time point, this

change failed to reach significance (Beavers et al., 2010). A similar response was observed after 6 months of structured aerobic and resistance training in elderly adults, in which average TNF-α and IL-6 concentrations, and CD3, CD4, and CD8 cell counts decreased with no sex-related differences (Abd El-Kader & Al-Jiffri, 2019; Abd El-Kader & Al-Shreef, 2018).

Proposed explanations for sex differences in the inflammatory response to acute exercise compared with chronic exercise may be linked to estrogen concentrations. Although some animal studies demonstrate that 17β-estradiol may help to alleviate muscle damage from exercise by influencing satellite cell activation and myoblast formation (Enns & Tiidus, 2008, 2010), this proposed explanation is not clear in human studies using exogenous estrogen treatment in healthy young men (MacNeil et al., 2011; Timmons, Hamadeh, & Tarnopolsky, 2006) . One study found that after 17β-estradiol treatment (1 mg for 2 days followed by 2 mg for 8 days) following a max eccentric exercise protocol (15 sets of 10 repetitions of leg extension and flexion), participants experienced attenuated neutrophil infiltration into rectus femoris myofibers and no changes in macrophage infiltration (MacNeil et al., 2011). However, another study found no changes in circulating neutrophil counts after 17β-estradiol treatment (2 mg/day for 8 days) following 90 minutes of cycling at 65% $\dot{V}O_2$ max (Timmons, Hamadeh & Tarnopolsky, 2006). Taken together, these studies suggest that there may be other mechanisms beyond estrogen signaling that contribute to sex differences in exercise-induced inflammation.

Sex Differences in Response to Physical Activity

Although research suggests a strong, negative correlation between physical activity and the incidence of chronic inflammation in both men and women, correlations with respect to sex-related differences in circulating inflammatory biomarkers are inconclusive (Pischon et al., 2003; Reuben et al., 2003; Taaffe et al., 2000). Healthy individuals (*n* = 405 males; *n* = 454 females)

ages 25-75 years old who reported more vigorous physical activity such as running, playing tennis, and calisthenics, appear to have a strong, negative correlation between energy expenditure from leisure-time physical activity, expressed as metabolic equivalent hours (METs), and plasma concentrations of tumor necrosis factor rector 1, soluble tumor necrosis factor receptor 2, IL-6, and CRP (Pischon et al., 2003). When adjusted for sex, women had significantly higher concentrations of tumor necrosis factor receptors than men, but there were no differences with respect to concentrations of IL-6 and CRP (Pischon et al., 2003). In older individuals (n = 412 males; n = 468 females) ages 70-79 years, physical activity, measured in hours of moderate and strenuous activity per year, was significantly correlated with lower concentrations of IL-6 and CRP (Taaffe et al., 2000). Sex-adjusted IL-6 concentrations were also significantly higher in men; however, no differences were found in concentrations of CRP (Taaffe et al., 2000).

Other large population studies consisting of older men and women also support the correlation between physical activity and lower concentrations of IL-6 and CRP, but these studies do not adjust for sex nor use accelerometers to measure average daily step counts (Colbert et al., 2004; Reuben et al., 2003). A cross-sectional study that measured physical activity using daily step counts in healthy individuals (n = 737 males; n = 1,101 females) ages 40-69 years old found that higher step counts were significantly correlated with lower circulating TNF-α concentration (Nishida et al., 2014). In the same study, men reported more moderate and vigorous intensity physical activity than women and also had greater IL-8 and TNF-α concentrations than women (Nishida et al., 2014). Though these studies provide evidence for the beneficial effect of physical activity on markers of chronic inflammation, they do not provide definitive evidence that benefits are equal in men and women.

Sex Differences in Cannabidiol Use and Response

Both survey and observational studies suggest that CBD use differs between males and females. In fact, most CBD users in both recreational and medicinal cannabis communities identify as women (BrightfieldGroup, 2017). An industry report of Americans (N = 2,400) that use cannabis revealed that 58% of CBD-only users were female and 59% of hemp-derived CBD users were female (BrightfieldGroup, 2017). The largest age group of CBD users were between 35-49 years old (33%) and the second largest age group of CBD users were between 26-34 years old (25%; BrightfieldGroup, 2017). When both sexes were combined, 80% of CBD-only users preferred vaping and 41% used CBD daily (BrightfieldGroup, 2017). These findings are similar to a more recently published survey with CBD-only users (n = 1,013 males; n = 1,087 females) which found that more females (67%, n = 729) used CBD for medical conditions compared to males (55%, n = 559), and that both sexes used CBD to help improve general health and wellbeing (Corroon & Phillips, 2018). Interestingly, the most reported medical condition associated with CBD use was chronic pain, but both reports did not stratify pain condition by sex (BrightfieldGroup, 2017). These data suggest that CBD is used as an alternative medicine for pain by both sexes with women using it more frequently.

Animal models designed to explore sex differences in CBD responses, have yielded mixed results. Sex-related differences are present in rodent models after administering CBD for pain (Linher-Melville et al., 2020) and models of neuropsychiatric disorders (Osborne, Solowij, Babic, et al., 2017; Osborne et al., 2019; Shbiro et al., 2019). Rodents exposed to peripheral nerve constriction injury benefited from i.p. CBD (25 mg/ml) treatment for 14 days after the injury which resulted in sex-related differences in pain perception 7 weeks following CBD treatment (Linher-Melville et al., 2020). More specifically, males experienced an alleviation of

mechanical hypersensitivity, but females were more hypersensitive and responded faster to mechanical pain on weeks 4, 5, and 6 post-treatment (Linher-Melville et al., 2020). In a rodent model of schizophrenia, i.p. CBD (20 mg/kg/day) treatment for 3 weeks resulted in improvements in working memory and social interaction of male rats (Osborne, Solowij, Babic, et al., 2017), and only working memory in female rats (Osborne et al., 2019). Other rodent experiments found no sex-related differences when CBD was administered for pain (Britch et al., 2020, 2017; Javadi-Paydar et al., 2018), leading researchers to hypothesize that small doses of THC may be needed in conjunction with CBD to have pain relieving effects. On the contrary, one recent rodent study that administered CBD and THC separately and combined found no sex differences in measures of pain and only the THC-treated rodents experienced an antinociceptive response (Britch et al., 2017). Very little progress has been made with respect to translating these studies to humans. In fact, there is a significant gap in the research related to the actions of CBD in men versus women. It is also necessary to recognize the importance of research related to the action of CBD in individuals who express different gender identities such as those who identify as transgender and/or transitioning as these groups may include a higher percentage of cannabis users (Hughto et al., 2021).

Although men and women tend to use CBD for the same reasons, there is lack of clarity with respect to potential sex-related differences in how CBD acts once inside the body. In fact, there are currently no studies investigating whether biological sex plays a role in mediating CBD-induced physiological responses. Just recently, the FDA Office of Women's Health virtual scientific conference "CBD & Other Cannabinoids, Sex and Gender Differences in Use and Responses" held November 19, 2020, from 9:00 a.m. to 4:00 p.m. Eastern Time, provided a platform for multiple perspectives on the issue (Food and Drug Administration, 2020). The

speakers and public officials represented various scientific fields including neuroscience, psychology, environmental health sciences, behavioral pharmacology, human behavior, biobehavioral sciences, pediatric and maternal health, cell biology, physiology, gynecology, reproductive sciences, and complementary and integrative health. Although informative, no firm conclusions regarding the efficacy and safety of CBD in humans without preexisting conditions and neurological disorders could be determined. Consequently, the FDA is now supporting further sex-related studies in healthy populations and agrees that more research is required to determine the potential benefits and risks of CBD use by both men and women.

Cognitive Health

Cognitive health is defined as the ability of an individual to perform mental processes such as memory, recall, judgement, and the ability to learn new things, and is inferred from behavior and response to cognitive assessments (Robbins, 2011). An assessment of cognitive health is frequently used as a measure of brain function in a wide variety of human populations. Cognitive neuroscience research has established frameworks and approaches to measure and compare cognition in different contexts including social and affective factors, disease states, and neural development (Greenwald et al., 1998; Robbins, 2011). In healthy individuals, cognitive function and ability are commonly inferred by responses to a neuropsychological battery of tests consisting of questions and tasks designed to gauge memory, recall, judgement, and the ability to learn new things (Borson et al., 2003; McDowell et al., 1997; Nasreddine et al., 2005). Cognitive impairment, which is defined as difficulty in remembering, learning new things, and concentrating is often included as a major outcome in cancer (Wefel et al., 2011), alcohol and substance abuse (Evert & Oscar-Berman, 1995), and mental health research (Stetz et al., 2007).

Cannabidiol and Cognitive Function

There is a plethora of animal research that demonstrates that CBD administration improves measures of cognitive impairment and mental health (Barichello et al., 2012; Campos et al., 2015; Mori et al., 2017; Osborne, Solowij, Babic, et al., 2017; Sales et al., 2020; Schiavon et al., 2016). Animal research shows i.p. CBD (10 mg/kg) treatment before and after cerebral ischemia result in less anxiety-like behavior in an open field test, improved memory and ability to recognize patterns from the spatial recognition test, and more exploration of new surroundings in mice (Mori et al., 2017), and 9 days i.p. CBD (10 mg/kg) treatment after inoculation with meningitis improves information retention and recall in a memory test in rodents (Barichello et al., 2012). Additionally, a rodent poly I:C model demonstrated that 3 weeks of i.p. CBD (20 mg/kg) treatment resulted in improved learning and memory (Osborne, Solowij, Babic, et al., 2017), and CBD-treated rats scored higher in the novel object recognition test and rewarded maze test compared to non-CBD treated rats (Osborne, Solowij, Babic, et al., 2017).

Cannabidiol may also be helpful in attenuating the side effects of other drugs. For example, 3 days of i.p. CBD (30 mg/kg) treatment along with the anti-malaria drug Artesunate in mice with cerebral malaria improved scores from the novel object recognition test, the elevated maze, and the water maze hidden platform test compared to Artesunate-only controls (Campos et al., 2015). This same study also found that CBD combined with Artesunate increased BDNF expression in the prefrontal cortex and decreased IL-6 and TNF-α concentrations in the hippocampus compared to the Artesunate-only and saline control groups (Campos et al., 2015). These findings suggest that CBD has a neuroprotective effect against cognitive impairment.

Although the effects of CBD on cognitive function are also reported in both clinical and non-clinical human populations, results are inconclusive. Clinical studies on patients with

schizophrenia suggest that CBD may affect cognitive function (Bhattacharyya et al., 2018; Boggs et al., 2018; McGuire et al., 2018; Osborne, Solowij, & Weston-Green, 2017). A 6-week adjunctive intervention with an oral solution of CBD (1000 mg/day) in patients with schizophrenia significantly improved scores on the Brief Assessment of Cognition in Schizophrenia test compared to the placebo group (McGuire et al., 2018). However, a similar study that administered oral CBD (600 mg/day) to patients with schizophrenia for 6 weeks found no significant changes in the Brief Assessment of Cognition in Schizophrenia test, verbal and visual learning tasks, and working memory tests (Boggs et al., 2018). When a single dose of CBD (300 and 600mg) was provided acutely in patients with schizophrenia, dosages failed to alter attention task performance (Hallak et al., 2010). These findings are in agreement with previous research that also found no changes in cognitive function after 4 weeks of CBD (150 mg/day) treatment in patients with Parkinson's Disease (Zuardi et al., 2009).

In individuals without disorders, research suggests that CBD may have protective effects against induced psychosis (Bhattacharyya et al., 2010; Bloomfield et al., 2020) and anxiety (Crippa et al., 2004). An MRI study in healthy men given both THC and CBD found that a single dose of oral CBD (600 mg) attenuated THC-induced psychosis and retained cognitive function (Bhattacharyya et al., 2010). The same study also observed increased blood flow to the prefrontal cortex, amygdala, and hippocampus during verbal memory and response inhibition tasks (Bhattacharyya et al., 2010). Another study supports the findings related to CBD-induced changes in blood flow in healthy individuals (Bloomfield et al., 2020). In this study, a single dose of oral CBD (600 mg) significantly increased cerebral blood flow to the hippocampus, but there were no differences in memory tasks between CBD and placebo groups (Bloomfield et al., 2020). Other neuroimaging studies provide evidence that acute oral CBD (400 mg)

administration increases cerebral blood flow specifically in the amygdala, hippocampus, and posterior cingulate gyrus of healthy men (Crippa et al., 2004). Although these studies suggest that CBD confers neuroprotective effects, more studies are needed to provide a consensus on the action of CBD in healthy individuals.

Cannabidiol, Cognitive Function, and Sex Differences

Animal literature suggests that there are sex differences in response to CBD with respect to cognitive function and behavior (Jimenez Naranjo et al., 2019; Osborne, Solowij, Babic, et al., 2017; Osborne et al., 2019; Osborne, Solowij, & Weston-Green, 2017). In the aforementioned male poly I:C rat model that demonstrated CBD-treated males improved cognitive function by scoring higher in cognitive and behavioral tests compared to non-CBD treated males (Osborne, Solowij, Babic, et al., 2017), a second follow-up study by the same authors using females found that females exhibited deficits in recognition memory and social interaction, but not working memory (Osborne et al., 2019). Additionally, only recognition memory and social interaction were improved by CBD treatment in females (Osborne et al., 2019). In a third follow-up study by the same authors, analyses between males and females revealed that concentrations and densities of neuronal markers acetylcholine esterase and choline acetyltransferase were significantly correlated with the rewarded maze performance scores in CBD-treated females, and concentrations of choline acetyltransferase were significantly correlated with maze test performance scores in CBD-treated males (Jimenez Naranjo et al., 2019).

In human studies, cannabis research shows sex differences in response to cannabis use on cognitive function (Crane, Schuster, Fusar-Poli, et al., 2013; Crane, Schuster, & Gonzalez, 2013; Crane et al., 2015; Matheson et al., 2020), but very few have evaluated sex differences in response to CBD (Schoedel et al., 2018; Spindle et al., 2020). A within-subjects crossover design

evaluating the pharmacokinetics of acute oral and vaporized CBD (100 mg) found that men performed worse on cognitive tasks than women after both oral and vaporized CBD were consumed (Spindle et al., 2020). Although participants (n = 9 males; n = 9 females) were healthy, there were no sex differences in cognitive task performance (Spindle et al., 2020). This response is similar to another crossover, phase 1, single-dose study designed to assess the therapeutic dose and abuse potential of highly purified oral CBD (Epidiolex, 750 mg, 1500 mg, and 4500 mg) (Schoedel et al., 2018). No differences in cognitive and psychomotor tasks were observed in healthy men and women regardless of CBD dose (Schoedel et al., 2018). When CBD use was analyzed with sex as a covariate, there were significant differences in verbal learning test scores between men and women; however, the specific dose of CBD and degree of difference were not reported (Schoedel et al., 2018). Although other pharmacokinetic research investigating the safety and tolerability of acute doses of CBD includes even numbers of men and women, they do not report sex-related analyses of CBD on cognitive function (Arndt & de Wit, 2017; Babalonis et al., 2017; Haney et al., 2016). Taken together, schizophrenia rodent models (poly I:C) suggest that CBD affects regions of the brain related to memory and learning, and these effects are influenced by sex. In humans, it is possible that healthy men and women may also experience changes in cognitive function after acute CBD administration though it is difficult to draw conclusions from the studies currently available. There are currently no longitudinal studies which explore the potential for biological sex to play a role in mediating the physiological and psychological responses to CBD.

Conclusions

Decades of research have focused on exploring the physiological and psychological effects of CBD in animal models and human populations. Animal studies suggest that there are

sex differences in inflammatory and behavioral responses to CBD, but these studies are focused on neurological models of depression (Sales et al., 2019; Shbiro et al., 2019), schizophrenia (Osborne, Solowij, Babic, et al., 2017; Osborne et al., 2019; Osborne, Solowij, & Weston-Green, 2017), and acute injury (Linher-Melville et al., 2020). A few human studies have come close to establishing a relationship between CBD and health (Arndt & de Wit, 2017; Babalonis et al., 2017; Bhattacharyya et al., 2010; Carlini & Cunha, 1981; Consroe et al., 1986; Crane, Schuter, & Conzalez, 2013; Cuñetti et al., 2018; Haney et al., 2016; Laczkovics et al., 2020; Leweke et al., 2012; Lisano et al., 2020; Martin-Santos et al., 2012; McGuire et al., 2018; Schräder et al., 2019; Solowij et al., 2018). However, these studies exclude females (Bhattacharyya et al., 2010; Crane, Schuster, & Gonzalez, 2013; Martin-Santos et al., 2012; Solowij et al., 2018), THC-free CBD (Crane, Schuster, & Gonzalez, 2013; Lisano et al., 2020; Solowij et al., 2018), do not analyze data by sex (Arndt & de Wit, 2017; Babalonis et al., 2017; Haney et al., 2016), and do not focus on the effects of CBD in healthy individuals (Carlini & Cunha, 1981; Consroe et al., 1986; Laczkovics et al., 2020; Leweke et al., 2012). Currently, there are no studies investigating the mechanisms associated with potential sex-related physiological responses to CBD in healthy individuals. There is no literature exploring the potential relationship as it relates to the inflammatory biomarkers IL-6 and CRP, as well as the neural health biomarker BDNF. Furthermore, these responses have not been linked to cognitive function and psychological wellbeing (PWB) in healthy and physically active adults. There are 295 CBD trials in the recruiting phase on clinicaltrials.gov to date where CBD is being used for various conditions including coronavirus, alcohol and substance use disorders, chronic pain, inflammatory bowel disorders and Crohn’s Disease, and various neuropsychiatric and neurological disorders. Only 31 related clinicaltrials.gov studies using CBD are recruiting healthy participants. They are focused

on determining drug interactions, pharmacokinetics, bioavailability, safety, and tolerability of CBD, as well as potential CBD-induced changes in autonomic, emotional, and cognitive function.

Although these findings are fascinating, the relationships among CBD inflammatory cytokines, BDNF, and cognitive function are still not clearly understood in healthy humans and non-stressed animal models. There is a great need for understanding the safety and efficacy of daily CBD treatment in healthy males and females who are not diagnosed with neuropsychiatric conditions. Research matching CBD use patterns is needed because observational and prospective studies suggest that females tend to use hemp-derived and highly purified CBD more than males (BrightfieldGroup, 2017; Corroon & Phillips, 2018). Consequently, these findings suggest that healthy physically active males and females may differ in response to CBD which may affect concentrations of IL-6, CRP, and BDNF, and subsequent cognitive function and PWB.

CHAPTER III

METHODOLOGY

Participants

The purpose of this double blind, placebo-controlled, clinical trial with parallel group design was to investigate the biological sex-related differences in physical activity patterns, health-related fitness, mental and cognitive health before and after an 8-week cannabidiol (CBD) intervention. This study also aimed to explore whether 8 weeks of CBD treatment would significantly alter biomarkers of inflammation and neural health.

Adult males and females were recruited into two groups, a CBD intervention group (CG) and a placebo group (PG) through flyers and word of mouth at the University of Northern Colorado and nearby communities. Individuals met eligibility requirements including an age range of 18 to 50 years, 6 weeks of abstinence from cannabis (either tetrahydrocannabinol (THC) and/or CBD), a body mass index (BMI) of ≤ 29.9 kg/m^2, and additional inclusion criteria requirements outlined in Table 1. Eligible participants were also free from significant cardiovascular disorders, neurological and severe mood and anxiety disorders, chronic alcohol and/or drug use, and no head trauma with loss of consciousness for more than 30 minutes.

Table 1

Inclusion and Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
18-50 years old BMI ≤ 29.9 kg/m^2.	Significant cardiovascular disorders including but not limited to serious arrythmias, cardiomyopathy, congestive heart failure, stroke, or transient ischemic attacks, peripheral vascular disease with intermittent claudication, acute, chronic, or recurrent thrombophlebitis.
Abstained from THC and/or CBD for 6 weeks.	Diagnosed neurological disorders including but not limited to brain tumors, brain injuries, Alzheimer's Disease, Parkinson's Disease, multiple sclerosis, epilepsy, and seizures.
Able and willing to commit to an 8-week intervention schedule.	Regular use of drugs that significantly alter brain activity such as selective serotonin reuptake inhibitors, benzodiazepines, and others used to treat anxiety, panic, stress, sleep disorders, or increases the risk of sedation and drowsiness.

Note. BMI = body mass index, THC = delta-9-tetrahydrocannabinol, CBD = cannabidiol.

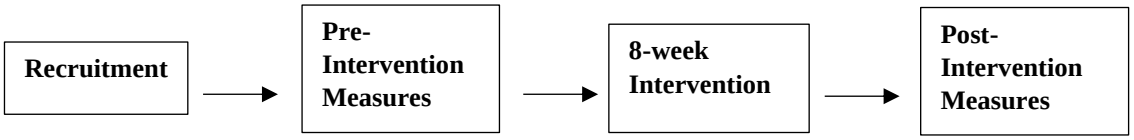
Study Overview

Participants completed a total of 8 visits consisting of 4 pre- and 4 post-intervention visits separated by an 8-week intervention period (Figure 1). During the first pre-intervention visit, participants were asked to review and sign the informed consent form approved by the University of Northern Colorado Institution Review Board. Participants reviewed the risks and benefits of participation as described on the form, and a copy was provided for them to keep. Participants were given an activity tracker (Fitbit, San Francisco, CA) to wear for 7 days before the 8-week intervention. Then, they completed an 8-hr fasted blood draw, cognitive function and psychological wellbeing (PWB) scales, and body size and composition assessments. During the pre-intervention Visits 2-4, participants completed a cardiorespiratory fitness assessment

measuring their relative peak oxygen uptake assessment ($\dot{V}O_2$ peak), the Wingate anaerobic fitness assessment measuring their anaerobic power outputs including peak power (PP), mean power (MP), relative peak power (RPP), relative mean power (RMP), and anaerobic fatigue (AF), and a muscular strength assessment measuring their bench press one repetition maximum (BP 1RM) and back squat one repetition maximum (BS 1RM). During the 8-wk intervention, participants received two, 7-day pill boxes with each slot containing either one liquid gel of 50 mg of purified, hemp-derived CBD (Six Degrees Wellness, Boulder, CO), to consume per day, or one capsule of 225 mg of medium-chain triglyceride (MCT; Nutiva, Point Richmond, CA) as a calorie-matched placebo. Participants were instructed to consume the one capsule of either the CBD or the MCT nightly, after dinner and before bed. Participants were asked to meet every 2 weeks with the investigator to refill the pill boxes, report any sickness and/or injury, and to report any changes in exercise routine. During week 7, participants were asked to wear their activity trackers for one final week. They then completed post-intervention Visits 5-8 consisting of the same measures as the pre-intervention visits. Study participants were not offered monetary compensation for their time and effort.

Figure 1

Study Overview



Pre-Intervention Measures *Week 00, Visit 1*	8-week Intervention *Weeks 1-7*	Post-Intervention Measures *Week 8* *Visits 5-8*
1. Consent form, Fasted blood draw, Surveys, Body size and composition assessments, and Fitbit Assignment *Week 0, Visits 2-4* 2. $\dot{V}O_2$ peak assessment 3. Anaerobic fitness assessment 4. 1RM assessment	• Weekly pill box refills • Weekly sickness and injury, and physical activity reports • *Week 7*: Fitbit Assignment	5. Fasted blood draw, Surveys, and Body size and composition assessments 6. $\dot{V}O_2$ peak assessment 7. Anaerobic fitness assessment 8. 1RM assessment

Note. $\dot{V}O_2$ = oxygen uptake; 1RM = one repetition maximum.

Visit 1 and Visit 5: Informed Consent, Blood Draw, Body Size and Composition Assessment, Surveys, and Physical Activity Measures

Blood Samples

After participants reviewed and signed the informed consent form in Visit 1, an 8-hr fasted blood sample was collected, and again at the beginning of Visit 5. Blood was collected into serum separator tubes (SST; Beckton Dickinson, East Rutherford, NJ, USA) by a certified phlebotomist through venipuncture of the antecubital vein of the forearm. Prior to blood collection in Visit 1, participants were asked to record their diets for the previous 24 hours and were asked to follow the same diet prior to the post-intervention Visit 5 blood sample. Whole blood collected in the SST tubes were positioned vertically in a tube rack and allowed to clot for at least 30 minutes and no more than 1 hour at room temperature. The SST tube was centrifuged

at 2000 *g* for 15 minutes at room temperature and serum was pipetted into 1.5 mL Eppendorf tubes (Eppendorf AG, Hamburg, Germany) and immediately stored in a -80°C freezer.

Serum concentrations of the inflammatory biomarker C-reactive protein (CRP) and peripheral concentrations of serum brain-derived neurotrophic factor (BDNF) were determined with commercially available enzyme-linked immunosorbent assay kits (ELISA; CRP, (ALPCO Diagnostics, Salem, NH, USA); BDNF (RayBiotech, Norcross, GA, USA)) for each respective biomarker. Manufacturer inter- and intra-assay coefficient of variabilities (CV) for serum concentrations of CRP were <6.7% and <9.9%, respectively, and for serum concentrations of BDNF were < 12% and <10%, respectively. These CVs were used to compare precision and repeatability of immunoassay test results. Microplates were read with a ELx800 BioTek microplate reader at the recommended wavelength of 450 nm (BioTek Instruments, Inc., Winooski, VT, USA).

Body Size and Composition Analysis

Participants were instructed to remove their shoes, socks, and excess clothing during height and weight measurements. Height was measured using a stadiometer (SECA 220, Chino, CA, USA) and weight was measured using a digital scale (Detecto, Webb City, MO, USA). Height, body mass (BM), lean body mass (LBM) and body fat percentage (BF%), were evaluated with air displacement plethysmography using a calibrated BodPod and predicted thoracic gas volumes (Cosmed Inc., Concord, CA, USA; Dempster & Aitkens, 1995).

Cognitive Function Scale

Subjective cognitive function was evaluated by using the National Institute of Health Patient-Reported Outcomes Measurement Information System (NIH PROMIS) Cognitive Function–Abilities–Short Form 8a. The 8-item survey indicated perceived level of functional

ability regarding concentration and memory (Valentine et al., 2019). Objective cognitive function was measured with the NIH PROMIS Cognitive Function–Short Form 8a, and assessed mental acuity, concentration, memory, and attention in 8 items (Valentine et al., 2019). Raw scores from both short forms were reported as T scores using the NIH PROMIS grading tool (Rothrock et al., 2020).

Psychological Wellbeing Scale

The psychological wellbeing (PWB) scale, also known as the Mental Health Continuum-Short Form (Jovanović, 2015), is an 18-item, 6-minute scale that measures six aspects of wellbeing and happiness: autonomy, environmental mastery, personal growth, positive relation with others, purpose in life, and self-acceptance (Ryff & Keyes, 1995). Participants rated how strongly they agreed or disagreed with each subscale on a 7-point Likert scale, and scores were determined by summing all items with each subscale. Higher scores indicated greater wellbeing.

Pre- and Post-Intervention Physical Activity

Participants were given an activity tracker (Fitbit Inspire Heart Rate Fitness Tracker, Fitbit, San Francisco, CA) to wear on their non-dominant wrist with notifications to move purposefully turned off, and black tape covering the face of the tracker. Participants were instructed to wear the tracker at all hours during the pre-intervention week (identified as Week 00 in Figure 1), and during week 7 of the 8-week intervention (Week 7 in Figure 1) to capture the potential effects of supplement consumption on physical activity measures. To offer an in-depth examination of physical activity and movement behavior, average daily steps and average distance traveled were recorded from the activity tracker. In both activity tracking time periods, subjects were asked to maintain their normal exercise routines.

Visit 2 and Visit 6: Cardiorespiratory Fitness Testing

To ensure participants were well hydrated prior to the cardiorespiratory fitness test, hydration was assessed with a urine specific gravity refractometer (Atago, Tokyo, Japan). If the urine sample had a urine specific gravity ≥ 1.020 mg/dL, participants were instructed to drink water and retest. If participants remained dehydrated, cardiorespiratory fitness testing was rescheduled.

Peak oxygen uptake ($\dot{V}O_2$ peak) was evaluated with a customized protocol using the Parvomedics TrueOne metabolic cart (Parvomedics, Sandy, UT, USA). The assessment was performed on a treadmill (Trackmaster, Full Vision Inc., Newton, KS, USA) with participants wearing a heart rate monitor (Polar Electro Inc., Bethpage, NY, USA) and fitted gas collection mask connected to the metabolic cart. Participants completed a customized protocol based on the directives provided by the American College of Sports Medicine Guidelines (ACSM) for multistage exercise testing including an initial warm-up period at low workload followed by progressive graded exercise with increasing loads, and with 2-minute stages (Pescatello et al., 2014). A customized protocol was chosen due to the large increments in workload (treadmill incline) between stages in the standard Bruce protocol. The customized protocol for testing $\dot{V}O_2$ peak was selected based of the modified Åstrand test, which compares favorably to the Bruce, Balke, and Ellestad protocols (Beltz et al., 2016; Pollock et al., 1976). The protocol consists of a 5-minute warmup at 3.5 mph with 0% incline, a 2-minute self-selected pace for a 5 km run at 0% incline, and 2-minute stages consisting of variations in treadmill speed and incline until volitional fatigue has been reached (Table 2). Heart rate, blood pressure, blood lactate, and rate of perceived exertion were measured at the end of each 2-minute stage (Borg, 1982).

Table 2

Customized Peak Oxygen Uptake Protocol

Stage	Speed (mph)	Grade (%)	Time (mins)
Warm Up	3.5	0	5
1	SS	0	2
2	SS + 1	0	2
3	(SS + 1) +1	0	2
4	Stage 3 speed	2	2
5	Stage 3 speed	4	2
6	Stage 3 speed	6	2
7	Stage 3 speed	8	2

Note. Mph = miles per hour, SS = self-selected pace in mph, mins = minutes.

Visit 3 and Visit 7: Anaerobic Fitness Testing

Peak power, mean power, and anaerobic fatigue were assessed with the 30-second Wingate test (Bar-Or, 1987) on a cycle ergometer (Monark, Varberg, Sweden). Participants began with a 5-minute warmup by cycling between 60-75 revolutions per minute at a self-selected resistance. After the warmup, the resistance was removed, 7.5% of the participant's body weight was added to the weight basket of the cycle ergometer, and the participant was instructed to pedal as fast as they could. Once participants reached max pedal cadence, the weight basket was released, and the test began. Participants cycled for a total of 30 seconds as hard and as fast as possible. After the 30 second test, participants completed a 5-minute cooldown for with a self-selected resistance.

Visit 4 and Visit 8: Muscular Strength Testing

Muscular strength was assessed with a one repetition maximum (1RM) test for the bench press (BP) followed by the back squat (BS) exercise to measure upper and lower body muscular strength. Strength testing guidelines set forth by the National Strength and Conditioning Association (NSCA) were used to conduct 1RM testing (Baechle & Earle, 2008). Briefly, the warm-up consisted of an unloaded barbell (1 set of 8-10 reps), followed by a warm-up consisting of 40-60% of the body weight added to the bar (1 set of 3-5 reps), and a final warm-up of 90-95% of body weight added to the bar (1 set of 1-2 reps). Participants were asked to rest for at least 2 minutes and no more than 4 minutes in between 1RM attempts. Participants were required to squat to parallel which is defined as the position where the top of the thighs are parallel to the floor. Rate of perceived exertion was asked to assist in deciding how much weight to add to the bar within 5–20-pound increments. Weight was only added to achieve 100% of each participant's 1RM. If the participant successfully completed the lift at this weight, additional weight was added in a conservative fashion until the participant failed to lift the weight. To ensure safety during all 1RM testing, participants were spotted by a trained exercise professional in accordance with NSCA spotting techniques, and with additional spot bars implemented in the lifting cage.

Cannabidiol Intervention Period

After completing all baseline and physiological characteristic measurements in the week prior to supplementation, participants were randomly assigned to the CBD (CG) or placebo (PG) intervention groups to ensure an even number of 12 males and 12 females per group: males consuming CBD (CG-M), females consuming CBD (CG-F), males consuming placebo (PG-M), and females consuming placebo (PG-F). Both participants and investigators were blinded to the

intervention groups. Participants were given two, 7-day pill boxes which supplied 14 capsules of either 50 mg of CBD or a calorie-matched placebo. These pill boxes were refilled biweekly throughout the 8-week intervention period. Participants were instructed to consume one pill once per day after dinner and before bed. Randomization was conducted by the principal investigator in a parallel design to determine superiority or equivalence to reduce systematic error bias and assessment bias by the experimenters. The principal investigator was also chosen to ensure blinding between research participants and the experimenters who will administer the treatment, collect the data, and analyze the outcomes.

Statistical Analyses

This study addressed the following research questions:

Q1 Is there a difference by sex or by treatment with respect to physical activity patterns, health-related fitness, measures of mental and cognitive health, and concentrations of CRP and BDNF?

Q2 Does 8 weeks of CBD affect physical activity patterns, health-related fitness, measures of cognitive and mental health, and resting concentrations of CRP and BDNF?

To address the first research question, an independent-samples t-test was used to compare means of each outcome by biological sex and treatment at the pre-intervention time point. The independent t-test was chosen over the paired-samples t-test because both sexes and treatments were independent of each other (participants in the male and female groups, and in CG and PG were separate individuals). The first independent samples t-test included one independent, categorical variable (sex) with two levels (males and females), and the second independent samples t-test included one, independent, categorical variable (treatment) with two levels (CG and PG). The multiple, continuous, dependent variables consisted of health-related fitness

measures, physical activity patterns, mental health, cognitive function, and resting concentrations of CRP and BDNF.

More specifically, these variables included the following: physical characteristics and resting heart rate and blood pressure (age, resting systolic blood pressure (RSBP), resting diastolic blood pressure (RDBP), and resting heart rate (RHR)), physical activity patterns (average steps and distance per day), body size and composition measurements (height, BM, BMI, LBM, and BF%), cardiorespiratory fitness (relative $\dot{V}O_2$peak), muscular strength (BP 1RM and BS 1RM), mental health (PWB scores in the autonomy, environmental mastery, personal growth, positive relation with others, purpose in life, and self-acceptance aspects), cognitive health (NIH PROMIS cognitive function T scores and cognitive function abilities T scores), absolute and relative anaerobic capacity (PP, MP, RPP, and RMP, and AF) and resting concentrations of CRP and BDNF.

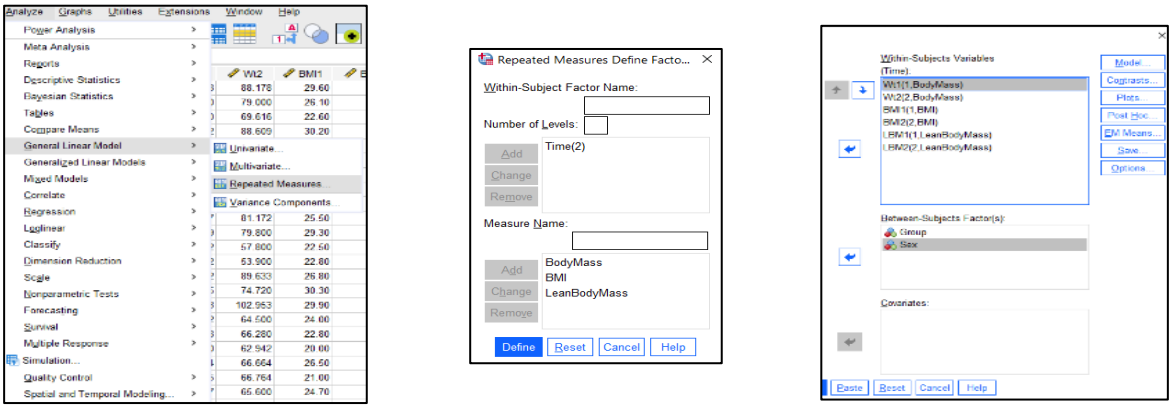
Data were assessed for normality and outliers by the Shapiro-Wilks test ($p > 0.05$), boxplot inspection, and Q-Q plots. No more than 10% of data were removed if significant outliers were detected (± 2.5 standard deviations from the mean). Independent t-tests were run on the data with a 95% confidence interval for the mean difference with significance set to $p < 0.05$. All statistical analyses were performed using SPSS 25 (IBM, Corp., Chicago, IL). Effect sizes (Cohen's d) were used to assess the magnitude of change for the independent samples t-tests, and values of 0.2, 0.5 and 0.8 were considered small, medium, and large effects, respectively. Effect sizes (partial eta squared "η^2") were also used to assess the magnitude of change in the 2-way analysis of variance (ANOVA), and values of 0.01, 0.06 and 0.14 were considered small, medium, and large effects, respectively.

To address the second research question, a 3-way ANOVA consisting of one categorical within-subjects factor (time: pre-/post-intervention) and two categorical between-subjects factors (sex: male/female; treatment: CBD/placebo) was used to understand if there were interactions (time * treatment * sex) on multiple continuous, dependent variables over time. A 3-way mixed ANOVA was chosen over a 2-way repeated measures ANOVA because there were three categorical factors: one within-subjects factor (two different time points) and two between-subjects factors (sex and treatment), whereas a 2-way repeated measures ANOVA required two categorical, within-subject factors (such as more than two time points or more than two genders). The 3-way mixed ANOVA model was built using a General Linear Model "Repeated Measures" and inputting "Time" as the within-subjects factor with 2 levels, and sex and treatment as between-subject factors (Figure 2).

Data were assessed for outliers by boxplot inspection and Q-Q plots and were removed if significant outliers were detected (± 2.5 standard deviations from the mean). Normality was assessed by the Shapiro-Wilk's test ($p > 0.05$), homogeneity by Levene's test for equality of variances ($p > 0.05$), and sphericity by Mauchly's test of sphericity ($p > 0.05$). Pairwise comparisons were performed with the Bonferroni post hoc test where significant interactions were detected. The Bonferroni corrected p value was calculated by dividing the original p value by the number of comparisons being performed. Partial eta squared was also used to assess the magnitude of change in mixed ANOVA model.

Figure 2

3-Way Mixed Analysis of Variance Model



Note. Mixed ANOVA model. The creation of the model in SPSS using body mass (Wt), body mass index (BMI), and lean body mass (LBM) measures as an example for the body size and composition analysis.

To avoid Type I error and achieve a desired level of 0.80 power with an $\alpha = 0.05$, an *a priori* analysis (G*Power, Dusseldorf, Germany) showed that a total sample size of 36 was needed. Means and standard deviations of between pre- and post-exercise intervention CRP concentrations in healthy young adults were used for computational analyses (Stewart et al., 2007). The total number of study participants was increased to 48 to maximize potential detection in differences. Each group was divided as follows: males consuming CBD (CG-M), $n = 12$; females consuming CBD (CG-F), $n = 12$; males consuming placebo (PG-M), $n = 12$; and females consuming placebo (PG-F), $n = 13$.

CHAPTER IV

RESULTS

The purpose of this double blind, placebo-controlled, clinical trial with parallel group design was to investigate the biological sex-related differences in physical activity patterns, health-related fitness, mental and cognitive health before and after an 8-week cannabidiol (CBD) intervention. This study also aimed to explore whether 8 weeks of CBD treatment would significantly alter biomarkers of inflammation and neural health.

Participants

Age and Ethnicity

A total of 64 individuals from campus and nearby communities were recruited but a total of 49 participants completed the study. Twenty-four participants were in the CBD group (CG) and 25 were in the placebo group (PG). Overall, there were 12 in the CBD male group (CG-M), 12 in the placebo male group (PG-M), 12 in the CBD female group (CG-F), and 13 in the placebo female group (PG-F). Overall mean age was 25.5 ± 5.7 years and ranged from 18 to 42 years. Mean age for CG was 24.3 ± 4.5 years and ranged from 18 to 36 years while the mean age for PG was 26.6 ± 6.6 years and ranged 20 to 42 years. There were no significant differences between treatment assignment groups $t(47) = -1.409$, $p = 0.165$, $d = -0.403$. Overall mean age for females and males was 25.4 ± 6.7 and 25.5 ± 4.5 years, respectively, and there were no significant differences between groups $t(47) = 0.011$, $p = 0.991$, $d = 0.003$. When age was analyzed by a 2-way analysis of variance (ANOVA; (treatment assignment * sex), there were no significant interactions $F(1, 45) = 1.497$, $p = 0.228$, $\eta^2 = 0.032$.

Most participants identified as Caucasian (61%; n = 30) with others identifying as Hispanic (12%; *n* = 6), Latino (4%; n = 2), Asian Pacific Islander (2%; *n* = 1), Native American (2%; *n* = 1), "other" (2%; *n* = 1), and "more than one race/ethnicity" (12%; *n* = 6). These individuals identified as African American and Caucasian, Asian Pacific Island and Caucasian, Hispanic and Latino, Hispanic and Caucasian, Asian and Caucasian, and Hispanic and Latina.

Self-Reported Physical Activity

Results from the International Physical Activity Questionnaire (IPAQ) revealed that there was a sex-related difference in which males reported 44% more time spent engaged in vigorous physical activity than females ($p = 0.043$), and females reported 24% more days walking than males ($p = 0.001$) at the pre-intervention time point (Table 3). There were no other significant sex differences with respect to days engaged in vigorous physical activity, days and time spent engaged in moderate physical activity, and time spent walking and sitting between males and females at the pre-intervention time point. There was a significant treatment difference in which PG reported 19% more days walking than CG ($p < 0.001$) at the pre-intervention time point (Table 4). There were no other significant treatment differences with respect to days and time spent engaged in moderate and vigorous physical activity, and time spent walking and sitting between CG and PG at the pre-intervention time point. When IPAQ responses were analyzed with a 2-way ANOVA (treatment assignment * sex), there were no significant interactions (Table 5). However, there was a main effect of sex in which females spent an overall of 44% more days walking than males at the pre-intervention time point ($p = 0.043$).

Table 3

Self-Reported Physical Activity Within the Last 7 Days by Sex

Pre-Physical Activity	Males ± *SD* (*n*)	Females ± *SD* (*n*)	Overall ± *SD* (*N*)	*p*	Cohen's *d*
Vigorous (days)	4.1 ± 1.6 (24)	3 ± 2.3 (24)	3.5 ± 2 (48)	0.063	0.551
Time spent in vigorous (mins)	74 ± 47.5 (24)	47.8 ± 38.4 (23)	61.2 ± 44.8 (47)	0.043 [a]	0.606
Moderate (days)	4.4 ± 2 (23)	3.5 ± 2.5 (24)	3.9 ± 2.3 (47)	0.165	0.411
Time spent in moderate (mins)	59.1 ± 34.7 (22)	47.9 ± 37.2 (24)	53.3 ± 36.1 (46)	0.299	0.310
Walking (days)	5.5 ± 2 (23)	7 ± 0 (20)	6.1 ± 1.6 (43)	0.001 [b]	-1.078
Time spent walking (mins)	82.1 ± 75.4 (21)	100.6 ± 106.4 (24)	92.1 ± 91.7 (45)	0.507	-0.196
Time spent sitting (hours)	5.1 ± 2 (20)	6.5 ± 3.6 (24)	5.8 ± 3 (44)	0.110	-0.494

[a] Denotes mean time spent in vigorous physical activity was significantly greater in males compared with females and [b] Denotes mean days spent walking was significantly greater in females than in males.

Table 4

Self-Reported Physical Activity Within the Last 7 Days by Treatment

Pre-Physical Activity	Cannabidiol Group (CG) ± *SD* (*n*)	Placebo Group (PG) ± *SD* (*n*)	Overall ± *SD* (*N*)	*p*	Cohen's *d*
Vigorous (days)	3.7 ± 1.9 (23)	3.4 ± 2.2 (25)	3.5 ± 2 (48)	0.618	0.145
Time spent in vigorous (mins)	64.6 ± 48.8 (23)	57.9 ± 41.3 (24)	61.2 ± 44.8 (47)	0.616	0.0147
Moderate (days)	3.9 ± 2.3 (22)	3.9 ± 2.4 (25)	3.9 ± 2.3 (47)	0.987	-0.005
Time spent in moderate (mins)	51.6 ± 33.5 (22)	54.8 ± 38.9 (24)	53.3 ± 36.1 (46)	0.767	-0.088
Walking (days)	5.8 ± 1.5 (23)	7 ± 0 (20)	6.3 ± 1.3 (43)	< 0.001 [a]	-1.103
Time spent walking (mins)	80.5 ± 83 (21)	107.3 ± 118.9 (23)	84.7 ± 78.9 (44)	0.392	-0.259
Time spent sitting (hours)	5.3 ± 2.2 (21)	5.8 ± 2.8 (22)	5. ± 3.3 (44)	0.981	0.007

Note. There were no treatment differences and [a] Denotes mean days spent walking was significantly greater in PG than in CG.

Table 5

Self-Reported Physical Activity Within the Last 7 Days by Treatment and Sex

	± *SD*				
Pre-Physical Activity	Cannabidiol Group-Male (CG-M) (*n* = 8)	Cannabidiol Group-Female (CG-F) (*n* = 11)	Placebo Group-Male (PG-M) (*n* = 10)	Placebo Group-Female (PG-F) (*n* = 10)	Overall (*N* = 39)
Vigorous (days)	3.7 ± 2	3.5 ± 2	3.3 ± 1.9	3.4 ± 2.3	3.5 ± 2
Time spent in vigorous (mins)	63.8 ± 33.8	40 ± 26.7	67 ± 46.4	54 ± 41.6	55.4 ± 37.9
Moderate (days)	2.9 ± 2.5	4.5 ± 2	3.3 ± 2.3	4.4 ± 2.6	3.8 ± 2.3
Time spent in moderate (mins)	40 ± 32.5	54.1 ± 28.9	57.5 ± 45.8	45.5 ± 34.4	49.9 ± 35.2
Walking (days)	5.8 ± 1.1	6.2 ± 1.2 [a]	5.2 ± 2.2	7 ± 0 [a]	6 ± 1.5
Time spent walking (mins)	42.5 ± 33.7	113.6 ± 102	131 ± 160.9	84.5 ± 70.2	96 ± 106.3
Time spent sitting (hours)	7.3 ± 4.3	4.9 ± 2.7	6.1 ± 3	6 ± 2.9	6 ± 3.2

[a] Denotes mean days spent walking was significantly greater in females than in males ($p = 0.043$).

Medication, Surgeries, and Medical History

Almost all participants were not consuming any prescribed therapeutic medications over the duration of the study (98%; *n* = 48). Only one male participant was currently taking medication at the pre-intervention time point (Zoloft, 50 mg/day) and later discontinued its use during the intervention period. Fifteen of the 25 female participants (60%; *n* = 15) were using a birth control method consisting of either an intrauterine device (*n* = 3) or oral contraceptive (*n* = 12) during the time of the study. Thirteen of the 25 female participants, (52%, CG-F: *n* = 6; PG-F: *n* = 7) began pre-intervention testing during their follicular phase in the menstrual cycle which was estimated from their disclosed ovulation cycle and last menses start date.

Approximately half of the participants (49%; *n* = 24) had at least one surgery with the remainder having more than one surgery (15%; *n* = 9), and no prior surgeries (33%, *n* = 16). Previous surgeries within a 29-year time frame included knee surgery (*n* = 4), wisdom tooth extraction (*n* = 3), tonsillectomy (*n* = 3), appendectomy (*n* = 3), Cesarean section (*n* =3), cholecystectomy (*n* = 2), lasik (*n* = 2), ankle surgery (*n* = 2), hip surgery (*n* = 2), hand and/or wrist surgery (*n* = 2), anterior cruciate ligament reconstruction (*n* = 2), labrum repair (*n* = 1), pilonidal cyst removal (*n* = 1), augmentation mammoplasty (*n* = 1), rhinoplasty (*n* = 1), tympanostomy (*n* = 1), facial surgery (*n* = 1), adenoidectomy (*n* = 1), sinus reconstruction (n = 1), and elbow surgery (*n* = 1). The most recent surgery was lasik (year 2020) and the oldest was tympanostomy (year 1996). Participants did not report any long-term discomforts or complications from previous surgery and were able to complete all study visits.

Medical history included presence of any past medical conditions such as disease, illness, diagnosis, therapy, and allergy. More than half the participants (57%; *n* = 28) had no previous medical history, less than half (29%; *n* = 14) had at least one previous medical condition, and a few (14%; *n* = 7) had more than one previous medical condition. Medical history included asthma (*n* = 7), diagnosis and treatment of depression (*n* = 6), streptococcal pharyngitis (*n* = 3), high blood cholesterol and/or triglycerides (*n* = 3), high blood pressure (*n* = 2), irritable bowel syndrome (*n* = 2), concussion (*n* = 1), kidney failure (*n* = 1), gestational diabetes (*n* = 1), herpes type 1 (*n* = 1), typhoid fever (*n* = 1), back pain (*n* = 1), and acid reflux (*n* = 1). The most recent medical conditions were occasional depression and sporadic irritable bowel syndrome (year 2021), and the oldest was acid reflux (year 1993). Participants with high blood cholesterol and/or triglycerides and high blood pressure reported no current diagnoses at the start of the study.

Participants also reported no conflicts from previous medical conditions and were able to compete all study visits.

Retention and Attrition Rates

Overall retention rate, calculated as the number of participants who completed the study divided by the number of participants that were recruited at the beginning of the study, times 100 ((49/64) *100), was 77% for a 17-month period. Overall attrition rate, calculated as the number of participants that left divided by the number of participants that started, times 100 [(15/49) *100], was 32%. Eleven of the 15 individuals who dropped out (73% of dropouts) did not complete the pre-intervention visits for the following reasons: having no time to complete visits (*n* = 2), experiencing an eating disorder trigger (*n* = 2), no reason and/or communication (n = 2), mental health issues (*n* = 1), formation of a medically induced ulcer (*n* = 1), pain in foot (*n* = 1), and knee pain (*n* = 1). Two individuals (13% of dropouts) left during the 8-week intervention period due to having no time to complete the rest of the study (*n* = 1) and no reason/communication (*n* = 1). Four individuals (27% of dropouts) completed the intervention but did not return for post-intervention testing due to having no time. Pre-intervention measures were completed for all participants except #56 (CG-M) who was unable to complete the anaerobic Wingate test before starting the supplement intervention due to a busy work schedule. Post-intervention measures were completed for all participants except for participants #32 (PG-M) and #48 (CG-M) who were unable to complete cognitive function and PWB scales, participants #54 (CG-M) and #64 (PG-M) who were unable to complete cardiorespiratory fitness testing due to time constraints, and #59 (PG-M) who refused to have blood drawn due to extreme anxiety.

Adverse Events

One male participant (#55 of CG-M) reported experiencing uncomfortable skin rashes on arms and legs during the first week of the intervention period. The participant was given the option to discontinue and seek medical treatment if serious; however, the rashes subsided by week 2 and the participant decided to continue with the study. Another male participant (#59 of PG-M) experienced a vasovagal reaction during the Visit 5 blood draw in which he had temporary dizziness, light sweating, and paleness. The blood draw was immediately ended which resulted in no post-intervention blood sample and the participant was given water and snacks and monitored until the vasovagal reaction subsided. Two male participants (#1 of CG-M and #48 of CG-M) experienced emesis after completing the pre-intervention anaerobic Wingate test (#48) and post-intervention anaerobic Wingate test (#1 and #48). In each situation, participants were encouraged to complete a 10–20-minute cool down on the treadmill while having their heart rate and blood pressure monitored and given water and light snacks before leaving the testing center. There were no life-threatening incidents, hospitalizations, or other serious medical events through the duration of this study.

Resting Heart Rate and Blood Pressure

Pre-Intervention Comparisons

Mean resting heart rate (RHR), resting systolic blood pressure (RSBP), and resting diastolic blood pressure (RDBP) by sex and by treatment at the pre-intervention time point are presented in Tables 6 and 7, respectively. Overall RHR ranged from 42 to 98 bpm, RSBP ranged from 98 to 152 mmHg, and RDBP ranged from 58 to 100 mmHg when all groups were combined at the pre-intervention time point. There were significant sex-related differences with respect to RSBP and RDBP in which males had 6% higher RSBP and 7% higher RDBP than

females at the pre-intervention time point ($p = 0.025$ and $p = 0.034$, respectively). There were no significant differences between males and females with respect to RHR, and there were also no significant differences between CG and PG treatments at the pre-intervention time point. When these outcomes were analyzed with a 2-way ANOVA (treatment assignment * sex), no interactions were found on RHR $F(1, 44) = 0.875$, $p = 0.355$, $\eta^2 = 0.020$, RSBP $F(1, 43) = 0.046$, $p = 0.831$, $\eta^2 = 0.001$, and RDBP $F(1, 43) = 0.105$, $p = 0.748$, $\eta^2 = 0.002$ (Table 8). A main effect of sex was found with respect to RSBP and RDBP in which male RSBP and RDBP were 6% and 7% higher than mean female RSBP and RDBP ($p = 0.034$ and $p = 0.048$, respectively).

Table 6

Pre-Intervention Resting Heart Rate and Blood Pressure by Sex

Pre-Intervention Variable	Males ± *SD* (n)	Females ± *SD* (n)	Overall ± *SD* (N)	*p*	Cohen's *d*
Resting heart rate (RHR) (bpm)	69.0 ± 9.6 (23)	65.9 ± 9.8 (25)	67.4 ± 9.6 (48)	0.266	0.326
Resting systolic blood pressure (RSBP) (mmHg)	121.5 ± 9.5 (22)	114.9 ± 10.1 (25)	118.0 ± 10.3 (47)	0.025 [a]	0.675
Resting diastolic blood pressure (RDBP) (mmHg)	77.7 ± 6.9 (22)	72.8 ± 8.2 (25)	75.1 ± 8.0 (47)	0.034 [b]	0.640

[a] Denotes mean male RSBP was significantly greater than mean female RSBP and [b] Denotes mean male RDBP was significantly greater than mean female RDBP.

Table 7

Pre-Intervention Resting Heart Rate and Blood Pressure by Treatment

Pre-Intervention Variable	Cannabidiol Group (CG) ± *SD* (*n*)	Placebo Group (PG) ± *SD* (*n*)	Overall ± *SD* (*N*)	*p*	Cohen's *d*
Resting heart rate (RHR) (bpm)	68.8 ± 7.7 (23)	66.2 ± 11.1 (25)	67.5 ± 9.6 (48)	0.366	0.264
Resting systolic blood pressure (RSBP) (mmHg)	118.13 ± 9.4 (23)	118 ± 11.4 (24)	118 ± 10.3 (47)	0.955	0.016
Resting diastolic blood pressure (RDBP) (mmHg)	75.7 ± 8.8 (23)	74.6 ± 7.3 (24)	75.1 ± 8 (47)	0.652	0.132

Note. There were no significant treatment differences.

Table 8

Pre-Intervention Resting Heart Rate and Blood Pressure by Treatment

Pre-Intervention Variable	Cannabidiol Group-Male (CG-M) ± *SD* (*n*)	Cannabidiol Group-Female (CG-F) ± *SD* (*n*)	Placebo Group-Male (PG-M) ± *SD* (*n*)	Placebo Group-Female (PG-F) ± *SD* (*n*)	Overall ± *SD* (*N*)
Resting heart rate (RHR) (bpm)	68.7 ± 7.6 (10)	68.5 ± 8.4 (12)	69.3 ± 11.7 (10)	63.3 ± 11.2 (12)	67.3 ± 9.9 (44)
Resting systolic blood pressure (RSBP) (mmHg)	120.4 ± 6.6 (10) [a]	113 ± 7.9 (11)	122.3 ± 12.4 (10) [a]	114.6 ± 10.1 (13)	117.2 ± 9.9 (44)
Resting diastolic blood pressure (RDBP) (mmHg)	79.4 ± 4.2 (10) [b]	73.6 ± 10.3 (12)	77.6 ± 8.0 (10) [b]	72.0 ± 6.1 (13)	75.3 ± 7.9 (45)

[a] Denotes mean male RSBP was significantly higher than mean female RSBP ($p = 0.034$) and [b] Denotes mean male RDBP was significantly higher than mean female RDBP ($p = 0.048$).

Intervention-Related Outcomes

Mean RHR, RSBP, and RDBP by time point, treatment, and sex are presented in Table 9. There were no significant 3-way interactions (time * treatment * sex) with respect to RHR, RSBP, and RDBP. A significant 2-way interaction (time * treatment) was found with respect to RSBP ($p = 0.047$); however, the Bonferroni post hoc test did not detect significant between-group differences. There were no other significant 2-way interactions (time * treatment or time * sex) with respect to RHR and RDBP. There was a main effect of sex with respect to RSBP where males had 7% higher overall RSBP than females ($p < 0.001$). There was also a main effect of sex with respect to RDBP where males had 9% higher overall RDBP than females ($p < 0.001$). There were no other main effects of time or treatment with respect to RHR, RSBP, and RDBP.

Physical Activity Patterns

Pre-Intervention Comparisons

Mean 7-day steps per day and distance traveled by sex and by treatment at the pre-intervention time point are presented in Tables 10 and 11, respectively. Overall mean 7-day steps per day ranged from 6,272 to 24,971 and distance traveled ranged from 2.5 to 11 miles when all groups were combined at the pre-intervention time point. There were no significant sex-related differences with respect to each physical activity measure and there were no significant differences between CG and PG treatment at the pre-intervention time point. When average steps per day and distance traveled were analyzed by a 2-way ANOVA (treatment assignment * sex), no interactions or main effects were found with respect to steps per day $F(1, 45) = 1.256$, $p = 0.268$, $\eta^2 = 0.027$ and distance traveled $F(1, 45) = 2.062$, $p = 0.158$, $\eta^2 = 0.044$ (Table 12).

Table 9

Resting Heart Rate and Blood Pressure by Time, Treatment, and Sex

	Pre-Intervention				Post-Intervention			
Variable	Cannabidiol Group-Male (CG-M) ± *SD* (*n*)	Cannabidiol Group-Female (CG-F) ± *SD* (*n*)	Placebo Group-Male (PG-M) ± *SD* (*n*)	Placebo Group-Female (PG-F) ± *SD* (*n*)	Cannabidiol Group-Male (CG-M) ± *SD* (*n*)	Cannabidiol Group-Female (CG-F) ± *SD* (*n*)	Placebo Group-Male (PG-M) ± *SD* (*n*)	Placebo Group-Female (PG-F) ± *SD* (*n*)
Resting heart rate (RHR) (bpm)	68.7 ± 7.6 (10)	68.5 ± 8.4 (12)	69.3 ± 11.7 (10)	63.3 ± 11.2 (12)	68.3 ± 8.7 (10)	71.1 ± 10.6 (12)	71.1 ± 9.9 (10)	64.0 ± 6.3 (12)
Resting systolic blood pressure (RSBP) (mmHg)	120.4 ± 6.6 (10) [a]	113 ± 7.9 (11)	122.3 ± 12.4 (10) [a]	114.6 ± 10.1 (13)	127.4 ± 8.8 (10) [a]	113 ± 9.9 11)	120.4 ± 10.4 (10) [a]	111.6 ± 8.9 (13)
Resting diastolic blood pressure (RDBP) (mmHg)	68.3 ± 8.7 (10) [b]	71.1 ± 10.6 (12)	71.1 ± 9.9 (10) [b]	64.0 ± 6.3 (12)	81.2 ± 10 (10) [b]	74.8 ± 9.6 (12)	76.6 ± 8.6 (10) [b]	68.0 ± 7.5 (13)

[a] Denotes mean male RSBP was significantly greater than mean female RSBP ($p < 0.001$) and [b] Denotes mean male RDBP was significantly greater than mean female RDBP ($p < 0.001$).

Table 10

Pre-Intervention Steps Per Day and Distance by Sex

	± *SD*				
Pre-Intervention Variable	Males (*n* = 24)	Females (*n* = 25)	Overall (*N* = 47)	*p*	Cohen's *d*
Steps per day	11,028.1 ±3,893.4	11,581.7 ± 4,545	11,495 ± 4,193	0.650	-0.131
Distance (mi)	4.8 ± 1.7	4.9 ± 2.0	4.9 ± 1.9	0.886	-0.041

Note. Values represent a 7-day average of both steps per day and total distance traveled. There were no significant sex differences.

Table 11

Pre-Intervention Steps Per Day and Distance by Treatment

	± *SD*				
Pre-Intervention Variable	CG (*n* = 24)	PG (*n* = 25)	Overall (*N* = 49)	*p*	Cohen's *d*
Steps per day	11,613.9 ± 4,186.3	11,019.4 ± 4,286.3	11,310.6 ± 4,204	0.626	0.140
Distance (mi)	4.9 ± 1.9	4.8 ± 2	4.9 ± 1.9	0.856	0.052

Note. Values represent a 7-day average of both steps per day and total distance traveled. There were no significant sex differences.

Table 12

Pre-Intervention Steps Per Day and Distance by Treatment and Sex

	± *SD*				
Pre-Intervention Variable	Cannabidiol Group-Male (CG-M) (*n* = 11)	Cannabidiol Group-Female (CG-F) (*n* = 12)	Placebo Group-Male (PG-M) (*n* = 11)	Placebo Group-Female (PG-F) (*n* = 13)	Overall (*N* = 47)
Steps per day	12,526.4 ± 4,681.4	11,200.6 ± 3,654.7	10,266.5 ± 2,553.3	11,933.6 ± 5,366.8	11,495 ± 4,193
Distance (mi)	5.5 ± 2.1	4.5 ± 1.4	4.4 ± 1.0	5.2 ± 2.5	4.9 ± 1.9

Note. Values represent a 7-day average of both steps per day and total distance traveled. There were no significant interactions or main effects.

Intervention-Related Outcomes

Mean steps per day and distance traveled by time point, treatment, and sex are presented in Table 13. There were no significant 3-way interactions (time * treatment * sex), 2-way interactions (time * sex, time * treatment, and treatment * sex), and main effects (time, treatment, or sex) on mean 7-day steps per day and distance traveled.

Table 13

Pre-Intervention Steps Per Day and Distance by Time, Treatment, and Sex

		Steps Per Day	Distance (mi)
Variable	*n*	± *SD*	± *SD*
Pre-Intervention			
Males in the cannabidiol group (CG-M)	11	12,526.4 ± 4,681.4	5.5 ± 2.1
Females in the cannabidiol group (CG-F)	12	11,200.6 ± 3,654.7	4.5 ± 1.4
Males in the placebo group PG-M	11	10,266.5 ± 2,553.3	4.4 ± 1.0
Females in the placebo group (PG-F)	13	11,933.6 ± 5,366.8	5.2 ± 2.5
Post-Intervention			
Males in the cannabidiol group (CG-M)	11	12,172.7 ± 2,956.5	5.2 ± 1.3
Females in the cannabidiol group (CG-F)	12	9,527.7 ± 3,881.9	4.1 ± 1.8
Males in the placebo group PG-M	11	10,043.7 ± 2,406.2	4.4 ± 1.1
Females in the placebo group (PG-F)	13	11,416.1 ± 4,991.1	5.2 ± 2.0

Note. Values represent a 7-day average of both steps per day and total distance. There were no significant interactions or main effects.

Body Size and Composition Measures

Pre-Intervention Comparisons

Mean height ranged from 152 to 195 cm, body mass ranged from 49.48 to 106.41 kg, body mass index (BMI) ranged from 19.60 to 33.00 kg/m^2, lean body mass (LBM) ranged from 36.89 to 83.50 kg, and body fat percentage (BF%) ranged from 8.2 to 51.4% when all groups were combined at the pre-intervention time point. There were significant sex-related differences (Table 14). Males were 7.6% taller than females (p = < 0.001) and 16.5% heavier than females (p < 0.001). Lean body mass was 32% greater in males when compared to females (p < 0.001), and females had 53% more BF% than males (p = < 0.001). There were no significant sex-related

differences with respect to BMI ($p = 0.258$), and no significant treatment differences (Table 15). When body size and composition were analyzed by a 2-way ANOVA (treatment assignment * sex), there were no interactions with respect to height $F(1, 49) = 0.011$, $p = 0.918$, $\eta^2 = 0.000$, BM $F(1, 45) = .111$, $p = 0.740$, $\eta^2 = 0.002$, BMI $F(1, 44) = 1.333$, $p = 0.254$, $\eta^2 = 0.029$, LBM $F(1, 45) = 0.232$, $p = 0.632$, $\eta^2 = 0.005$, and BF% $F(1, 45) = 0.007$, $p = 0.932$, $\eta^2 = 0.000$ at the pre-intervention time point (Table 16). The 2-way ANOVA showed a main effect of sex was found with respect to height, BM, LBM, and BF% where males were 7.6% taller, 16.5% heavier, had 32% more LBM and 53% less BF than females ($p < 0.001$, $p < 0.001$, $p < 0.001$, and $p < 0.001$, respectively).

Table 14

Pre-Intervention Body Size and Composition Measures by Sex

Pre-Intervention Variable	Males ± *SD* (n)	Females ± *SD* (n)	Overall ± *SD* (N)	*p*	Cohen's *d*
Height (cm)	177 ± 7.0 (24)	164.4 ± 7.4 (25)	170.6 ± 9.6 (49)	<0.001 [a]	1.746
Body mass (BM) (kg)	79.8 ± 12.5 (24)	67.5 ± 12.3 (25)	73.5 ± 13.7 (49)	0.001 [b]	0.984
Body mass index (BMI) (kg/m^2)	25.4 ± 3.4 (24)	24.3 ± 3.0 (24)	24.8 ± 3.2 (48)	0.258	0.33
Lean body mass (LBM) (kg)	66.4 ± 7.9 (24)	48.1 ± 5.4 (25)	57.2 ± 11.5 (49)	<0.001 [c]	2.711
Body fat percentage (BF) (%)	15.9 ± 6.4 (24)	27.6 ± 8.5 (25)	21.2 ± 8.6 (49)	<0.001 [d]	-1.528

[a] Denotes males were significantly taller than females, [b] Denotes males had significantly more body mass than females, [c] Denotes males had significantly more lean body mass than females, and [d] Denotes females had significantly more body fat than males.

Table 15

Pre-Intervention Body Size and Composition Measures by Treatment

Pre-Intervention Variable	Cannabidiol Group (CG) ± *SD* (*n*)	Placebo Group (PG) ± *SD* (*n*)	Overall ± *SD* (*N*)	*p*	Cohen's *d*
Height (cm)	170.1 ± 9.7 (24)	171.2 ± 9.8 (25)	170.7 ± 9.7 (49)	0.700	-0.111
Body mass (BM) (kg)	73.9 ± 16.7 (24)	73.3 ± 10.6 (25)	73.6 ± 13.7 (49)	0.884	0.042
Body mass index (BMI) (kg/m^2)	24.7 ± 3.7 (23)	25 ± 2.8 (25)	24.9 ± 3.2 (48)	0.806	-0.071
Lean body mass (LBM) (kg)	56.8 ± 12.2 (24)	57.4 ± 10.9 (25)	57.1 ± 11.4 (49)	0.865	-0.049
Body fat percentage (BF) (%)	22.2 ± 10.2 (24)	21.6 ± 9.1 (25)	21.9 ± 9.6 (49)	0.825	0.063

Note. There were no significant treatment differences.

Table 16

Pre-Intervention Body Size and Composition Measures by Treatment and Sex

	± *SD*				
Pre-Intervention Variable	Cannabidiol Group-Male (CG-M) (*n* = 12)	Cannabidiol Group-Female (CG-F) (*n* = 11)	Placebo Group-Male (PG-M) (*n* = 12)	Placebo Group-Female (PG-F) (*n* = 13)	Overall (*N* = 48)
Height (cm)	176.4 ± 5.7 [a]	164.1 ± 9.3	178 ± 8.4 [a]	165 ± 6.3	170.9 ± 7.6
Body mass (BM) (kg)	80.6 ± 15.4 [b]	63.6 ± 10.3	79 ± 9.5 [b]	68 ± 8.8	72.9 ± 13.1
Body mass index (BMI) (kg/m^2)	25.8 ± 4	23.6 ± 3.1	25 ± 2.8	25 ± 3	24.9 ± 3.2
Lean body mass (LBM) (kg)	66.5 ± 9 [c]	46.8 ± 5.3	66.5 ± 7.1 [c]	49 ± 5.6	57.2 ± 11.5
Body fat percentage (BF) (%)	16.5 ± 7.9	25.8 ± 5.8 [d]	15.5 ± 4.9	27.3 ± 8.4 [d]	21.3 ± 8.6

[a] Denotes males were significantly taller than females ($p < 0.001$), [b] Denotes males had significantly more body mass than females ($p < 0.001$), [c] Denotes males had significantly more lean body mass than females ($p < 0.001$), and [d] Denotes females had significantly more body fat than males ($p < 0.001$).

Intervention-Related Outcomes

Mean BM, BMI, LBM, and BF by time point, treatment, and sex are presented in Table 17. There were no significant 3-way (time * treatment * sex) and 2-way (time * sex, time * treatment, and treatment * sex) interactions on body size and composition measures. However, there was a main effect of sex with respect to BM where males had 18% higher overall BM than females ($p = 0.001$), LBM where males had 28% higher overall LBM than females ($p < 0.001$), and overall BF% where females had 55% more body fat than males ($p < 0.001$).

Table 17

Mean Body Size and Composition Measures by Time, Treatment, and Sex

	Pre-Intervention				Post-Intervention			
Variable	Cannabidiol Group-Male (CG-M) ± *SD* (*n*)	Cannabidiol Group-Female (CG-F) ± *SD* (*n*)	Placebo Group-Male (PG-M) ± *SD* (*n*)	Placebo Group-Female (PG-F) ± *SD* (*n*)	Cannabidiol Group-Male (CG-M) ± *SD* (*n*)	Cannabidiol Group-Female (CG-F) ± *SD* (*n*)	Placebo Group-Male (PG-M) ± *SD* (*n*)	Placebo Group-Female (PG-F) ± *SD* (*n*)
Body mass (BM) (kg)	80.6 ± 15.3 (12) [a]	67.1 ± 15.7 (12)	79.0 ± 9.5 (12) [a]	67.9 ± 8.7 (13)	80.8 ± 15.3 (12) [a]	67.2 ± 15.8 (12)	79.4 ± 9.3 (12) [a]	67.8 ± 8.7 (13)
Body mass index (BMI) (kg/m^2)	25.8 ± 4.0 (12)	23.6 ± 3.0 (11)	25.0 ± 2.7 (12)	24.9 ± 2.9 (13)	26 ± 4.1 (12)	23.6 ± 3.1 (11)	25.1 ± 2.7 (12)	24.9 ± 2.9 (13)
Lean body mass (LBM) (kg)	66.5 ± 9.0 (12) [b]	47.1 ± 5.2 (12)	66.4 ± 7.0 (12) [b]	49.0 ± 5.6 (13)	66.7 ± 8.8 (12) [b]	50.3 ± 9.7 (12)	66.2 ± 7.4 (12) [b]	50.8 ± 10.5 (13)
Body fat percentage (BF) (%)	16.4 ± 7.9 (12)	27.9 ± 9.1 (12) [c]	15.4 ± 4.8 (12)	27.3 ± 8.3 (13) [c]	16.5 ± 7.9 (12)	28 ± 9.1 (12) [c]	16.4 ± 4.9 (12)	28.1 ± 8.3 (13) [c]

[a] Denotes mean male BM was significantly greater than mean female BM ($p < 0.001$), [b] Denotes mean male LBM was significantly greater than mean female LBM ($p < 0.001$), and [c] Denotes mean female BF was significantly greater than mean male BF ($p < 0.001$).

Cardiorespiratory Fitness and Muscular Strength Measures

Pre-Intervention Comparisons

Mean relative peak oxygen uptake ($\dot{V}O_2$ peak) and one repetition maximum (1RM) measures by sex and by treatment at the pre-intervention time point are presented in Tables 18 and 19, respectively. Overall relative $\dot{V}O_2$ peak ranged from 20 to 62.3 ml/kg/min, bench press (BP) 1RM ranged from 25 to 161 kg, and back squat (BS) 1RM ranged from 27 to 166 kg when all groups were combined at the pre-intervention time point. There were significant sex-related differences. The mean, relative $\dot{V}O_2$ peak in males was 14.7% higher when compared to the mean, relative $\dot{V}O_2$ peak in females ($p = 0.006$). Mean BP 1RM in males was 80% greater when compared to the mean BP 1RM in females ($p < 0.001$) and the mean BS 1RM in males was 46.4% greater when compared to the mean BS 1RM in females ($p < 0.001$). A 2-way ANOVA (treatment assignment * sex) revealed no significant interactions with respect to relative $\dot{V}O_2$ peak $F(1, 45) = 1.047$, $p = 0.312$, $\eta^2 = 0.023$, BP 1RM $F(1, 44) = 1.924$, $p = 0.940$, $\eta^2 = 0.000$, and BS 1RM $F(1, 44) = 0.059$, $p = 0.809$, $\eta^2 = 0.001$ (Table 20). There was a main effect of sex with respect to mean, relative $\dot{V}O_2$ peak, and BP and BS 1RM. Mean male relative $\dot{V}O_2$ peak, BP 1RM, and BS 1RM were 16%, 80%, and 46% greater than mean female relative $\dot{V}O_2$ peak, BP 1RM, and BS 1RM ($p = 0.011$, $p < 0.001$, and $p < 0.001$, respectively).

Table 18

Pre-Intervention Peak Oxygen Uptake, Bench Press One Repetition Maximum, and Back Squat One Repetition Maximum by Sex

Pre-Intervention Variable	Males ± *SD* (*n*)	Females ± *SD* (*n*)	Overall ± *SD* (*N*)	*p*	Cohen's *d*
Peak oxygen uptake ($\dot{V}O_2$ peak) (ml/min/kg)	47.4 ± 8.3 (24)	40.9 ± 7.6 (25)	44.1 ± 8.5 (49)	0.006 [a]	0.818
Bench press (1 repetition maximum) (BP 1RM) (kg)	93.4 ± 24.4 (23)	40.3 ± 8.6 (25)	65.7 ± 32.2 (48)	< 0.001 [b]	1.766
Bench squat (1 repetition maximum) (BS 1RM) (kg)	112.8 ± 25.1 (23)	70.2 ± 23.0 (25)	90.6 ± 32.1 (48)	< 0.001 [c]	2.942

[a] Denotes mean, relative $\dot{V}O_2$ peak was significantly greater in males than females, [b] Denotes mean bench press 1RM was significantly greater in males than females, and [c] Denotes mean back squat 1RM was significantly greater in males than females.

Table 19

Pre-Intervention Peak Oxygen Uptake, Bench Press One Repetition Maximum, and Back Squat One Repetition Maximum by Treatment

Pre-Intervention Variable	Cannabidiol Group (CG) ± *SD* (*n*)	Placebo Group (PG) ± *SD* (*n*)	Overall ± *SD* (*N*)	*p*	Cohen's *d*
Peak oxygen uptake ($\dot{V}O_2$ peak) (ml/min/kg)	68.8 ± 7.7 (23)	66.2 ± 11.1 (25)	67.5 ± 9.6 (48)	0.366	0.264
Bench press (1 repetition maximum) (BP 1RM) (kg)	118.13 ± 9.4 (23)	118 ± 11.4 (24)	118 ± 10.3 (47)	0.955	0.016
Bench squat (1 repetition maximum) (BS 1RM) (kg)	75.7 ± 8.8 (23)	74.6 ± 7.3 (24)	75.1 ± 8 (47)	0.652	0.132

Note. There were no significant treatment differences.

Table 20

Pre-Intervention Peak Oxygen Uptake, Bench Press One Repetition Maximum, and Back Squat One Repetition Maximum by Treatment and Sex

	± *SD*				
Pre-Intervention Variable	Cannabidiol Group-Male (CG-M) (*n=11*)	Cannabidiol Group-Female (CG-F) (*n=12*)	Placebo Group-Male (PG-M) (*n=12*)	Placebo Group-Female (PG-F) (*n=13*)	Overall (*N=48*)
Peak oxygen uptake ($\dot{V}O_2$ peak) (ml/min/kg)	48.5 ± 9.4 [a]	40.4 ± 8	45.6 ± 7 [a]	41.4 ± 7.6	43.9 ± 8.4
Bench press (1 repetition maximum) (BP 1RM) (kg)	91.9 ± 22.3 [b]	39.2 ± 8.7	94.9 ± 27.3 [b]	41.4 ± 8.9	65.8 ± 32.2
Bench squat (1 repetition maximum) (BS 1RM) (kg)	113 ± 21.7 [c]	72.2 ± 27	112.7 ± 29 [c]	68.5 ± 19.8	90.7 ± 32.1

[a] Denotes mean, relative $\dot{V}O_2$ peak was significantly greater in males than females ($p = 0.006$), [b] Denotes mean bench press 1RM was significantly greater in males than females ($p < 0.001$), and [c] Denotes mean back squat 1RM was significantly greater in males than females ($p < 0.001$).

Intervention-Related Outcomes

Mean, relative $\dot{V}O_2$ peak, and BP and BS 1RM values by time point, treatment, and sex are presented in Table 21. There were no significant 3-way (time * treatment * sex) and 2-way (time * sex, time * treatment, and treatment * sex) interactions with respect to mean, relative $\dot{V}O_2$ peak and BP and BS 1RM values. A main effect of time was found with respect to mean, relative $\dot{V}O_2$ peak and BS 1RM values. Overall mean, relative $\dot{V}O_2$ peak values decreased by 4% ($p = 0.035$) and BS 1RM values increased by 5.4% ($p = 0.027$) by the end of intervention. A main effect of sex was also found in which males had 18% higher overall mean, relative $\dot{V}O_2$ peak values, 80% higher overall mean BP 1RM values, and 45% higher overall mean BS 1RM values than females ($p = 0.003$, < 0.001, and < 0.001, respectively).

Table 21

Mean Relative Peak Oxygen Uptake, Bench Press One Repetition Maximum, and Back Squat One Repetition Maximum by Time, Treatment, and Sex

	Pre-Intervention				Post-Intervention			
Variable	Cannabidiol Group-Male (CG-M) ± *SD* (*n*)	Cannabidiol Group-Female (CG-F) ± *SD* (*n*)	Placebo Group-Male (PG-M) ± *SD* (*n*)	Placebo Group-Female (PG-F) ± *SD* (*n*)	Cannabidiol Group-Male (CG-M) ± *SD* (*n*)	Cannabidiol Group-Female (CG-F) ± *SD* (*n*)	Placebo Group-Male (PG-M) ± *SD* (*n*)	Placebo Group-Female (PG-F) ± *SD* (*n*)
Peak oxygen uptake ($\dot{V}O_2$ peak) (ml/min/kg)	49.3 ± 9.3 (12) [a]	40.4 ± 7.9 (12)	45.2 ± 7.6 (13) [a]	41.4 ± 7.5 (13)	47.8 ± 8.2 (12) [a, d]	38.9 ± 7.4 (12) [d]	46.2 ± 7.1 (10) [a, d]	39.8 ± 6.1 (13) [d]
Bench press (1 repetition maximum) (BP 1RM) (kg)	91.9 ± 22.2 (11) [b]	39.2 ± 8.7 (12)	94.8 ± 27.2 (12) [b]	41.3 ± 8.8 (13)	92.9 ± 21.8 (11) [b]	40.0 ± 9.2 (12)	96.7 ± 26.3 (12) [b]	40.8 ± 8.3 (13)
Bench squat (1 repetition maximum) (BS 1RM) (kg)	113 ± 21.6 (11) [c]	72.2 ± 26.9 ± (12)	112.7 ± 29 (12) [c]	68.4 ±19.7 (13)	116.4 ±22.8 (11) [c, e]	78.1 ± 24 (12) [e]	119.2 ± 22.6 (12) [c, e]	71.7 ± 19.6 (12) [e]

[a] Denotes mean, relative $\dot{V}O_2$ peak was significantly greater in males than females ($p = 0.003$), [b] Denotes mean bench press 1RM was significantly greater in males than females ($p < 0.001$), [c] Denotes mean back squat 1RM was significantly greater in males than females ($p < 0.001$), [d] Denotes post-intervention mean, relative $\dot{V}O_2$ peak values were significantly lower than pre-intervention values ($p = 0.035$), and [e] Denotes post-intervention mean back squat 1RM values were significantly greater than pre-intervention values ($p = 0.027$).

Anaerobic Fitness Measures

Pre-Intervention Comparisons

Mean peak power (PP), mean power (MP), relative peak power (RPP), and relative mean power (RMP) by sex and by treatment at the pre-intervention time point are presented in Tables 22 and 23, respectively. Overall mean PP ranged from 372.19 to 1147.73 W, MP ranged from 287.82 to 803.91 W, RPP ranged from 3.71 to 12.66 W/kg, RMP ranged from 2.85 to 8.37 W/kg, and AF ranged from 54.40 to 71.35% when all groups were combined at the pre-intervention time point. There was a significant sex-related difference in which males had 36% greater mean PP ($p < 0.001$), 39% greater mean MP ($p < 0.001$), 21% greater mean RPP ($p < 0.001$), and 20% greater mean RMP than females ($p < 0.001$). There were no significant sex-related differences with respect to AF. When mean PP, MP, RPP, RMP, and AF were analyzed with a 2-way ANOVA (treatment assignment * sex), no significant interactions were found on PP $F(1, 44) = 1.067$, $p = 0.307$, $\eta^2 = 0.024$, MP $F(1, 44) = 0.280$, $p = 0.600$, $\eta^2 = 0.006$, RPP $F(1, 44) = 0.353$, $p = 0.555$, $\eta^2 = 0.008$, RMP $F(1, 44) = 0.001$, $p = 0.979$, $\eta^2 = 0.000$, and AF $F(1, 44) = 0.574$, $p = 0.453$, $\eta^2 = 0.013$ (Table 24). There was a main effect of sex with respect to mean PP, MP, RPP, and RMP where males had 39%, 39%, 22%, and 20% greater values than females ($p < 0.001$, $p < 0.001$, $p < 0.001$, and $p < 0.001$, respectively).

Table 22

Pre-Intervention Anaerobic Fitness Measures by Sex

	± *SD*				
Pre-Intervention Variable	Males (*n* = 23)	Females (*n* = 25)	Overall (*N* = 48)	*p*	Cohen's *d*
Peak power (PP) (W)	811.2 ± 135.1	549.4 ± 104.3	674.8 ± 177.7	< 0.001 [a]	2.180
Mean power (MP) (W)	573.2 ± 107.4	388.2 ± 63	476.8 ± 127.1	< 0.001 [b]	2.123
Relative peak power (W/kg)	10.1 ± 1.3	8.2 ± 1.5	9.1 ± 1.7	< 0.001 [c]	1.294
Relative mean power (W/kg)	7.1 ± 1	5.8 ± 0.9	6.4 ± 1.2	< 0.001 [d]	1.275
Anaerobic fatigue (AF) (%)	54.4 ± 12.9	55.9 ± 6.9	55.2 ± 10.1	0.621	-0.144

[a] Denotes mean PP was significantly greater in males than females, [b] Denotes mean MP was significantly greater in males than females, [c] Denotes mean RPP was significantly greater in males than females, and [d] Denotes mean RMP was significantly greater in males than females.

Table 23

Pre-Intervention Anaerobic Fitness Measures by Treatment

	± *SD*				
Pre-Intervention Variable	Cannabidiol Group (CG) (*n* = 23)	Placebo Group (PG) (*n* = 25)	Overall (*N* = 48)	*p*	Cohen's *d*
Peak power (PP) (W)	672.4 ± 188.1	677.1 ± 171.5	675 ± 177	0.929	-0.026
Mean power (MP) (W)	477.1 ± 130.6	476.7 ± 126.6	476.9 ± 127.1	0.992	0.003
Relative peak power (RPP) (W/kg)	9.1 ± 1.9	9.1 ± 1.7	9.2 ± 1.7	0.873	-0.046
Relative mean power (RMP) (W/kg)	6.5 ± 1.3	6.4 ± 1.2	6.5 ± 1.2	0.937	0.023
Anaerobic fatigue (AF) (%)	56.6 ± 8.2	56 ± 5.9	56.3 ± 7.1	0.758	0.089

Note. There were no significant treatment differences.

Table 24

Pre-Intervention Anaerobic Fitness Measures by Treatment and Sex

	± *SD*				
Pre-Intervention Variable	Cannabidiol Group-Male (CG-M) (*n* = 11)	Cannabidiol Group-Female (CG-F) (*n* =12)	Placebo Group-Male (PG-M) (*n* = 12)	Placebo Group-Female (PG-F) (*n* = 13)	Overall (*N* = 48)
Peak power (PP) (W)	828.7 ± 111.4 [a]	529.2 ± 112.5	795.2 ± 157 [a]	568.1 ± 96.9	674.9 ± 177.7
Mean power (MP) (W)	580 ± 102.2 [b]	381.8 ± 62.5	566.1 ± 116.1 [b]	394.1 ± 65.4	476.9 ± 127.1
Relative peak power (RPP) (W/kg)	10.2 ± 1.4 [c]	8.1 ± 1.6	10.1 ± 1.4 [c]	8.4 ± 1.5	9.2 ± 1.7
Relative mean power (RMP) (W/kg)	7.1 ± 1.2 [d]	5.8 ± 1	7.1 ± 1 [d]	5.8 ± 0.9	6.5 ± 1.2
Anaerobic fatigue (AF) (%)	57 ± 8.4	56.3 ± 8.4	56.3 ± 6.6	55.6 ± 5.5	56.3 ± 7.1

[a] Denotes mean PP was significantly greater in males than females ($p < 0.001$), [b] Denotes mean MP was significantly greater in male than females ($p < 0.001$), [c] Denotes mean RPP was significantly greater in males than females ($p < 0.001$), and [d] Denotes mean RMP was significantly greater in males than females ($p < 0.001$).

Intervention-Related Outcomes

Mean PP, RPP, MP, RMP, and AF by time point, treatment, and sex are presented in Table 25. There were no significant 3-way interactions (time * treatment * sex) with respect to PP, RPP, MP, RMP, and AF. A significant 2-way interaction (time * treatment) was found with respect to mean PP ($p = 0.013$) and RPP ($p = 0.006$). A follow-up Bonferroni multiple comparison confirmed that PG experienced a 9% decrease in mean PP ($p = 0.006$) and 3% decrease in mean RPP compared to CG ($p = 0.006$) and CG experienced no changes in mean PP and RPP after the 8-week intervention (Figures 3 and 4, respectively). A significant 2-way interaction (time * sex) was also found with respect to mean MP and RMP ($p = 0.017$ and $p = 0.036$, respectively). Bonferroni post hoc testing confirmed that females experienced a 4.5% decrease in mean MP ($p = 0.021$) and a 3.5% decrease in mean RMP compared to males ($p = 0.018$) while males experienced no changes in mean MP and RMP after the 8-week intervention (Figures 5 and 6, respectively). A main effect of sex was found with respect to overall mean PP and RPP in which males had 40% and 22% higher overall mean PP and RPP than females ($p = <0.001$ and $p = < 0.001$, respectively). A main effect of sex was also found on overall MP and RMP in which males had 41% and 22% higher overall mean MP and RMP than females ($p = <0.001$ and $p = < 0.001$, respectively).

Table 25

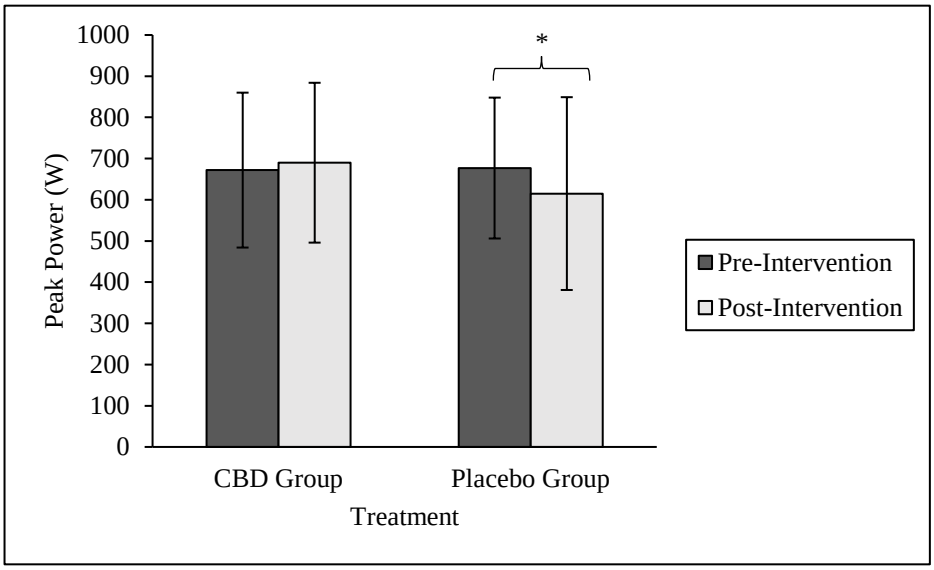
Mean Anaerobic Fitness Measures by Time, Treatment, and Sex

	Pre-Intervention				Post-Intervention			
	± *SD*				± *SD*			
Variable	Cannabidiol Group-Male (CG-M) (*n* = 11)	Cannabidiol Group-Female (CG-F) (*n* = 12)	Placebo Group-Male (PG-M) (*n* = 12)	Placebo Group-Female (PG-F) (*n* = 13)	Cannabidiol Group-Male (CG-M) (*n* = 11)	Cannabidiol Group-Female (CG-F) (*n* = 12)	Placebo Group-Male (PG-M) (*n* = 12)	Placebo Group-Female (PG-F) (*n* = 13)
Peak power (PP) (W)	828.7 ± 111.4 [e]	529.1 ± 112.5	795.1 ± 157 [a, e]	568.1 ± 96.8 [a]	852.4 ± 119.9 [e]	540.9 ± 107.8	724.6 ± 272.7 [a, e]	512.9 ± 133.6 [a]
Mean power (MP) (W)	10.2 ± 1.4 [f]	8 ± 1.6	10 ± 1.4 [b, f]	8.3 ± 1.51 [b]	10.4 ± 1.4 [f]	8.2 ± 1.8	9.5 ± 1.5 [b, f]	7.8 ± 1.4 [b]
Relative peak power (RPP) (W/kg)	580.9 ± 102.1 [g]	381.8 ± 62.5 [c]	566.7 ± 116.1 [g]	396.1 ± 54.4 [c]	593.1 ± 84.7 [g]	396.9 ± 65.5 [c]	571.3 ± 120.1 [g]	371.1 ± 73.9 [c]
Relative mean power (RMP) (W/kg)	7.1 ± 1.1 [h]	5.8 ± 1 [d]	7.1 ± 1 [h]	5.8 ± 0.9 [d]	7.2 ± 0.9 [h]	5.7 ± 1.2 [d]	7.1 ± 0.9 [h]	5.4 ± 0.9 [d]
Anaerobic fatigue (AF) (%)	52.4 ± 17.6	56.3 ± 8.4	56.3 ± 6.5	55.6 ± 5.5	58.3 ± 7.34	61.3 ± 8.8	55.3 ± 8.6	60.2 ± 9.2

[a] Denotes post-intervention mean PP was significantly lower in PG than CG ($p = 0.013$; Bonferroni: $p = 0.006$), [b] Denotes post-intervention mean RPP was significantly lower in PG than CG ($p = 0.006$; Bonferroni: $p = 0.006$), [c] Denotes post-intervention mean MP was significantly lower in females than males ($p = 0.017$; Bonferroni: $p = 0.021$), [d] Denotes post-intervention mean RMP was significantly lower in females than males ($p = 0.036$; Bonferroni: $p = 0.018$), [e] Denotes overall mean PP was significantly greater in males than females ($p < 0.001$), [f] Denotes overall mean RPP was significantly greater in males than females ($p < 0.001$), [g] Denotes overall mean MP was significantly greater in males than females ($p < 0.001$), and [h] Denotes overall mean RMP was significantly greater in males than in females ($p < 0.001$).

Figure 3

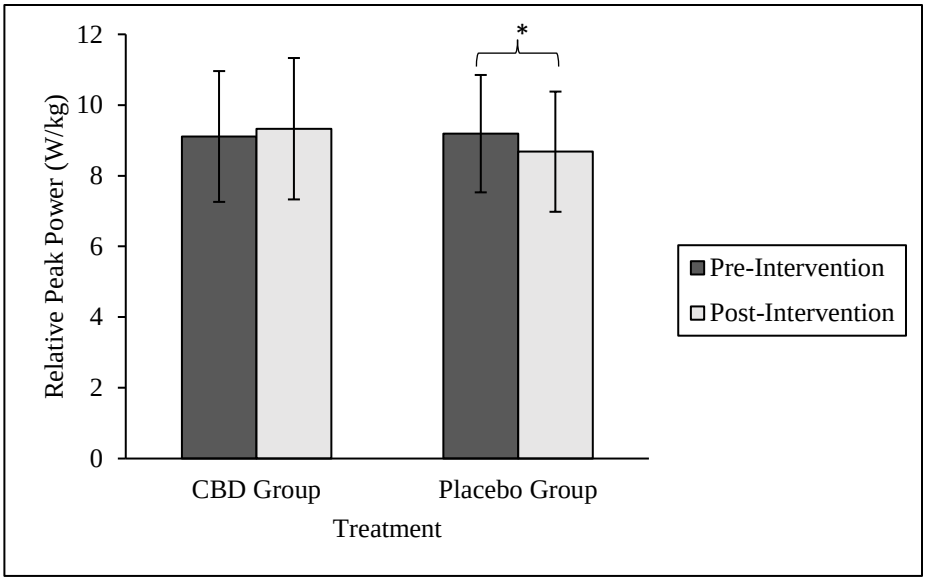
Pre- and Post-Intervention Peak Power by Treatment



* Denotes mean peak power at the post-intervention time point was significantly lower than the pre-intervention time point for PG (p = 0.006).

Figure 4

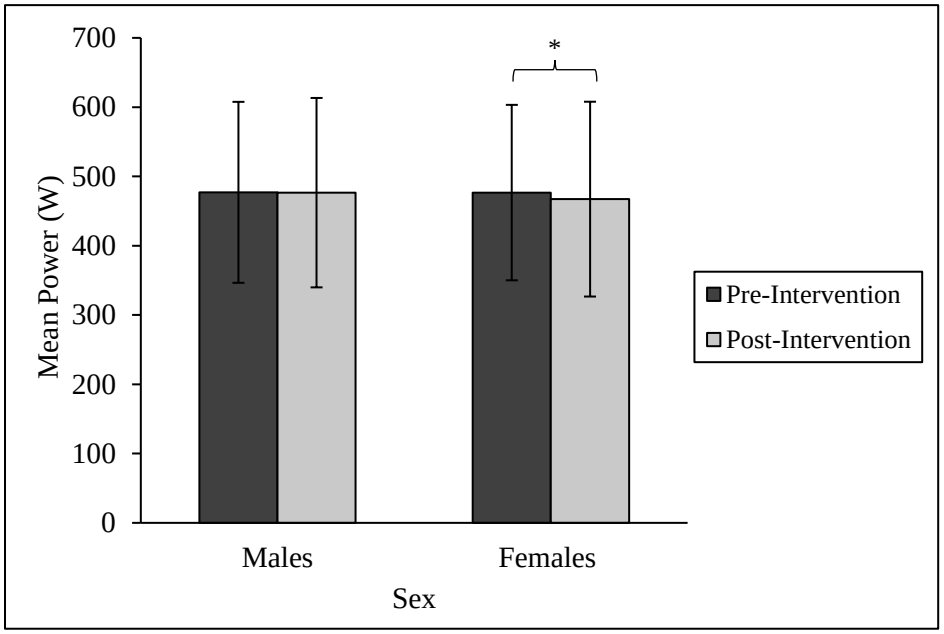
Pre- and Post-Intervention Relative Peak Power by Treatment



* Denotes relative mean peak power at the post-intervention time point was significantly lower than the pre-intervention time point for PG (p = 0.006).

Figure 5

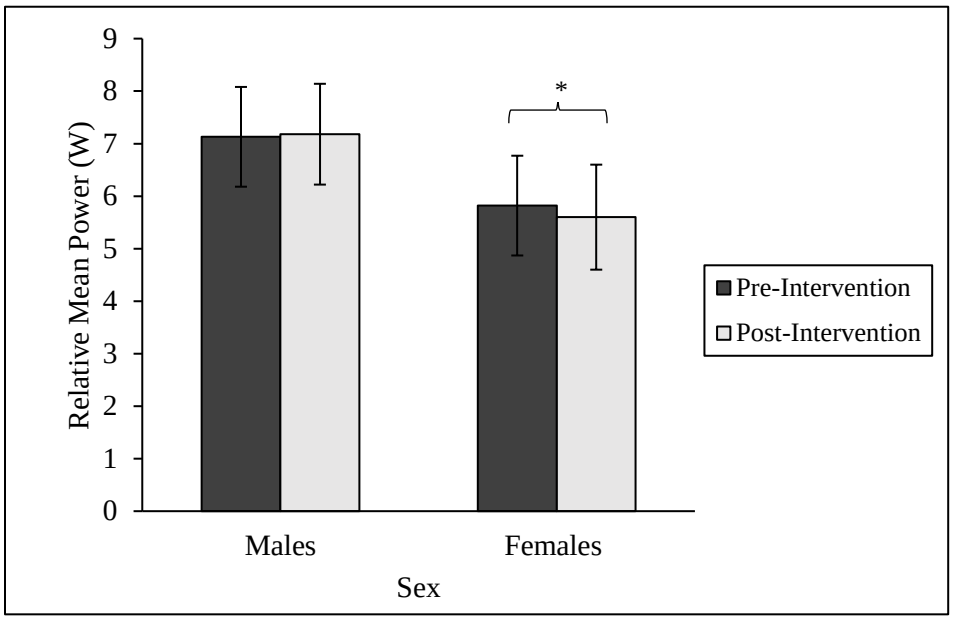
Pre- and Post-Intervention Mean Power by Sex



* Denotes relative mean power at the post-intervention time point was significantly lower than the pre-intervention time point for females ($p = 0.021$).

Figure 6

Pre- and Post-Intervention Relative Mean Power by Sex



* Denotes relative mean power at the post-intervention time point was significantly lower than the pre-intervention time point for females ($p = 0.018$).

Psychological Wellbeing

Pre-Intervention Comparisons

Mean psychological wellbeing (PWB) scores for each of the 6 aspects (autonomy, environmental mastery, personal growth, positive relation with others, purpose in life, and self-acceptance) by sex and by treatment at the pre-intervention time point are presented in Tables 26 and 27, respectively. Overall autonomy scores ranged from 8 to 21, environmental mastery scores ranged from 7 to 21, personal growth scores ranged from 15 to 21, positive relation with other scores ranged from 10 to 21, purpose in life scores ranged from 11 to 21, and self-acceptance scores ranged from 8 to 21. There was a significant sex-related difference with respect to purpose in life scores in which females had 7.7% higher scores than males ($p = 0.041$). There were no significant sex-related differences with respect to autonomy, environmental

mastery, personal growth, positive relation with others, and self-acceptance. There were also no significant treatment differences for and no 2-way (treatment assignment * sex) interactions or main effects for all PWB aspects ($F(1, 45) = 1.976$, $p = 0.167$, $\eta^2 = 042$, $F(1, 45) = 0.303$, $p = 0.585$, $\eta^2 = 0.007$, $F(1, 45) = 0.255$, $p = 0.616$, $\eta^2 = 0.006$, $F(1, 45) = 0.151$, $p = 0.699$, $\eta^2 = 0.003$, $F(1, 45) = 0.166$, $p = 0.686$, $\eta^2 = 0.004$, $F(1, 45) = 0.237$, $p = 0.628$, $\eta^2 = 0.005$, respectively; Table 28).

Table 26

Pre-Intervention Psychological Wellbeing by Sex

Pre-Intervention Variable	Males ± *SD* (*n*)	Females ± *SD* (*n*)	Overall ± *SD* (*N*)	*p*	Cohen's *d*
Autonomy	17 ± 3.1 (24)	16 ± 3 (25)	16.5 ± 3 (49)	0.273	0.317
Environmental Mastery	15.5 ± 3.1 (25)	15.7 ± 3.4 (25)	15.6 ± 3.3 (50)	0.849	-0.055
Personal Growth	20 ± 1.6 (24)	20.4 ± 0.9 (25)	20.2 ± 1.3 (49)	0.336	-0.280
Positive Relation with Others	17.5 ± 3 (24)	17.9 ± 3 (25)	17.7 ± 3 (49)	0.694	-0.113
Purpose in Life	16.9 ± 2.2 (24)	18.2 ± 2.2 (25)	17.6 ± 2.4 (49)	0.041 [a]	-0.600
Self-Acceptance	17.5 ± 3.2 (24)	17.9 ± 3.1 (25)	17.7 ± 3.1 (49)	0.612	-0.146

Note. Values represent participant scores for each aspect from a 7-point Likert scale of the Psychological Wellbeing Scale.

[a] Denotes mean purpose in life scores were significantly higher in females than males ($p = 0.041$).

Table 27

Pre-Intervention Psychological Wellbeing by Treatment

	± *SD*				
Pre-Intervention Variable	Cannabidiol Group (CG) (*n* = 24)	Placebo Group (PG) (*n* = 25)	Overall (*N* = 49)	*p*	Cohen's *d*
Autonomy	17 ± 3	16 ± 3.1	16.5 ± 3	0.273	0.317
Environmental Mastery	16.1 ± 2.8	15 ± 3.6	15.6 ± 3.3	0.307	0.295
Personal Growth	20.2 ± 1.2	20.2 ± 1.4	20.2 ± 1.3	0.929	-0.26
Positive Relation with Others	17.3 ± 3.1	18.1 ± 2.8	17.7 ± 3	0.384	-0.251
Purpose in Life	17.5 ± 2.6	17.8 ± 2.1	17.6 ± 2.4	0.658	-0.127
Self-Acceptance	17.6 ± 2.7	17.8 ± 3.6	17.7 ± 3.1	0.812	-0.060

Note. Values represent participant scores for each aspect from a 7-point Likert scale of the Psychological Wellbeing Scale. There were no significant treatment differences.

Table 28

Pre-Intervention Psychological Wellbeing by Treatment and Sex

	± *SD*				
Pre-Intervention Variable	Cannabidiol Group-Male (CG-M) (*n* = 12)	Cannabidiol Group-Female (CG-F) (*n* = 12)	Placebo Group-Male (PG-M) (*n* = 12)	Placebo Group-Female (PG-F) (*n* = 13)	Overall (*N* = 49)
Autonomy	18.1 ± 3	16 ± 2.7	16 ± 2.8	16.2 ± 3.4	16.5 ± 3
Environmental Mastery	16.3 ± 2.5	16.9 ± 3.2	14.8 ± 3.6	15.5 ± 3.8	15.6 ± 3.3
Personal Growth	20.1 ± 1.4	20.3 ± 0.9	20 ± 1.8	10.5 ± 0.9	20.2 ± 1.2
Positive Relation with Others	17 ± 3.5	17.7 ± 2.9	18.1 ± 2.5	18.1 ± 3.2	17.7 ± 2.9
Purpose in Life	16.9 ± 2.5	18 ± 2.7	16.9 ± 2.1	18.5 ± 1.9	17.6 ± 2.4
Self-Acceptance	17.6 ± 2.7	17.5 ± 2.7	17.3 ± 3.7	18.2 ± 3.6	17.7 ± 3.1

Note. Values represent participant scores for each aspect from a 7-point Likert scale of the Psychological Wellbeing Scale. There were no significant interactions or main effects.

Intervention-Related Outcomes

Mean PWB scores for each aspect by each time point, treatment, and sex are presented in Table 29. There were no significant 3-way (time * treatment * sex) and 2-way (time * sex, time * treatment, and treatment * sex) interactions on mean PWB scores for each aspect. There was main effect of time on mean personal growth, positive relation with others, purpose in life scores in which each significantly decreased by 5%, 7%, and 7% by the end of the intervention ($p < 0.001$, $p = 0.017$, and $p = 0.016$, respectively). A main effect of sex was also found with respect to mean purpose in life scores in which females had 11.7% scores than males ($p = 0.008$).

Cognitive Function

Pre-Intervention Comparisons

Mean cognitive function T scores and cognitive function abilities T scores by sex and by treatment at the pre-intervention time point are presented in Tables 30 and 31, respectively. Overall cognitive function T scores ranged from 29.8 to 63.9 and cognitive function ability T scores ranged from 36.9 to 67.1. There were no significant sex or treatment differences with respect to cognitive function and cognitive function abilities T scores. When these outcomes were analyzed by a 2-way ANOVA (treatment assignment * sex), there were no interactions or main effects were with respect to cognitive function T score $F(1, 45) = 0.923$, $p = 0.342$, $\eta^2 = 0.020$ and cognitive function abilities T scores $F(1, 45) = 0.412$, $p = 0.542$, $\eta^2 = 0.009$ (Table 32).

Table 29

Psychological Wellbeing by Time, Treatment, and Sex

	Pre-Intervention				Post-Intervention			
	± *SD*				± *SD*			
Variable	Cannabidiol Group-Male (CG-M) (*n* = 11)	Cannabidiol Group-Female (CG-F) (*n* = 12)	Placebo Group-Male (PG-M) (*n* = 11)	Placebo Group-Female (PG-F) (*n* = 13)	Cannabidiol Group-Male (CG-M) (*n* = 11)	Cannabidiol Group-Female (CG-F) (*n* = 12)	Placebo Group-Male (PG-M) (*n* = 11)	Placebo Group-Female (PG-F) (*n* = 13)
Autonomy	17.8 ± 3	15.9 ± 2.7	16.1 ± 2.9	16.1 ± 3.3	17.6 ± 2.3	15.7 ± 2.8	15.6 ± 3.6	15.9 ± 3.7
Environmental Mastery	16.3 ± 2.6	15.9 ± 3.2	15 ± 3.7	15.5 ± 3.8	15 ± 4.5	15.3 ± 3.1	14.9 ± 2.2	16 ± 4.5
Personal Growth	20 ± 1.4	20.2 ± 0.9	20.1 ± 1.8	20.5 ± 0.8	18.7 ± 2.8 [a]	19.3 ± 1.5 [a]	18.6 ± 3 [a]	20.1 ± 1.3 [a]
Positive Relation with Others	16.8 ± 3.6	17.7 ± 2.9	18.3 ± 2.5	18.1 ± 3.2	15.6 ± 3 [b]	17.9 ± 3 [b]	16 ± 3.1 [b]	17.5 ± 3 [b]
Purpose in Life	16.6 ± 2.4	18 ± 2.7 [d]	16.7 ± 2.1	18.5 ± 1.9 [d]	15.3 ± 3 [c]	17.3 ± 2.9 [c, d]	15.1 ± 4.3 [c]	17.9 ± 3.2 [c, d]
Self-Acceptance	17.4 ± 2.7	17.6 ± 2.7	17.5 ± 3.9	18.2 ± 3.6	17.5 ± 2.6	16.8 ± 2.3	16.9 ± 4.1	17.5 ± 3.2

Note. Values represent participant scores for each aspect from a 7-point Likert scale of the Psychological Wellbeing Scale.

[a] Denotes post-intervention mean personal growth scores were significantly lower than pre-intervention scores ($p < 0.001$), [b] Denotes post-intervention mean positive relation with other scores were significantly lower than pre-intervention scores ($p = 0.017$), [c] Denotes post-intervention mean purpose in life scores were significantly lower than pre-intervention scores ($p = 0.016$), and [d] Denotes mean purpose in life scores were significantly higher in females than males ($p = 0.008$).

Table 30

Pre-Intervention Cognitive Function T Scores by Sex

	± *SD*				
Pre-Intervention Variable	Males (*n* = 24)	Females (*n* = 25)	Overall (*N* = 49)	*p*	Cohen's *d*
Cognitive Function T Scores	49.8 ± 7.4	48.5 ± 8.8	49.1 ± 8.1	0.588	0.156
Cognitive Abilities T Scores	52.3 ± 8.6	51.1 ± 7.1	51.7 ± 7.8	0.616	0.144

Note. Values represent participant scores calculated from the 5-point Likert scale of each of the NIH PROMIS Cognitive Function Questionnaires. There were no significant sex differences.

Table 31

Pre-Intervention Cognitive Function T Scores by Treatment

	± *SD*				
Pre-Intervention Variable	Cannabidiol Group (CG) (*n* = 24)	Placebo Group (PG) (*n* = 25)	Overall (*N* = 49)	*p*	Cohen's *d*
Cognitive Function T Scores	50.1 ± 6.6	48.2 ± 9.4	49.1 ± 8.1	0.102	0.220
Cognitive Abilities T Scores	51.8 ± 7.1	51.6 ± 8.7	51.7 ± 7.8	0.394	0.035

Note. Values represent participant scores calculated from the 5-point Likert scale of each of the NIH PROMIS Cognitive Function Questionnaires. There were no significant treatment differences.

Table 32

Pre-Intervention Cognitive Function T Scores by Treatment and Sex

	± *SD*				
Pre-Intervention Variable	Cannabidiol Group-Male (CG-M) (*n* = 11)	Cannabidiol Group-Female (CG-F) (*n* = 12)	Placebo Group-Male (PG-M) (*n* = 11)	Placebo Group-Female (PG-F) (*n* = 13)	Overall (*N* = 47)
Cognitive Function T Scores	51.7 ± 7.2	48.3 ± 6.0	47.9 ± 8.0	48.7 ± 11.1	4.0 ± 8.1
Cognitive Abilities T Scores	53.0 ± 9.1	50.5 ± 5.1	51.3 ± 9.2	51.7 ± 8.8	51.6 ± 8.0

Note. Values represent participant scores calculated from the 5-point Likert scale of each of the NIH PROMIS Cognitive Function Questionnaires. There were no significant group differences.

Intervention-Related Outcomes

Mean cognitive function T scores and cognitive function abilities T scores by each time point, treatment, and sex are presented in Table 33. There were no significant 3-way interactions (time * treatment * sex), 2-way interactions (time * sex, time * treatment, and treatment * sex), and main effects (time, treatment, and sex) with respect to both cognitive function T scores and cognitive function abilities T scores.

Table 33

Mean Cognitive Function T Scores by Time, Treatment, and Sex

	Pre-Intervention				Post-Intervention			
	± *SD*				± *SD*			
Variable	Cannabidiol Group-Male (CG-M) (*n* = 11)	Cannabidiol Group-Female (CG-F) (*n* = 12)	Placebo Group-Male (PG-M) (*n* = 11)	Placebo Group-Female (PG-F) (*n* = 13)	Cannabidiol Group-Male (CG-M) (*n* = 11)	Cannabidiol Group-Female (CG-F) (*n* = 12)	Placebo Group-Male (PG-M) (*n* = 11)	Placebo Group-Female (PG-F) (*n* = 13)
Cognitive Function T Scores	51.7 ± 7.2	48.3 ± 6.0	47.9 ± 8.0	48.7 ± 11.1	49.8 ± 6.5	48.4 ± 7.2	49.6 ± 9.7	46.2 ± 13.4
Cognitive Abilities T Scores	53.0 ± 9.1	50.5 ± 5.1	51.3 ± 9.2	51.7 ± 8.8	51.1 ± 8.8	52.7 ± 8.0	52.7 ± 9.1	50.0 ± 14.5

Note. Values represent participant scores calculated from the 5-point Likert scale of each of the NIH PROMIS Cognitive Function Questionnaires. There were no significant interactions or main effects.

Resting Concentrations of C-Reactive Protein

Pre-Intervention Comparisons

Mean concentrations of C-reactive protein (CRP) by sex and by treatment at the pre-intervention time point are presented in Tables 34 and 35, respectively. Overall concentrations of CRP ranged from 0.1 to 8.8 mg/L when all groups were combined at the pre-intervention time point and there were no significant differences between sex and treatment. A 2-way ANOVA (treatment assignment * sex) found no interactions or main effects with respect to concentrations of CRP at the pre-intervention time point; however, a medium effect size was detected $F(1, 42) = 4.089$, $p = 0.050$, $\eta^2 = 0.089$ showing that CG-F had 81% higher concentrations of CRP than PG-F (Table 36). The inter- and intra-assay CVs for serum concentrations of CRP were 11.78% and 3.5%, respectively, and both were within manufacturer ranges.

Intervention-Related Outcomes

Mean concentrations of CRP at the pre- and post-intervention time points are presented in Figure 7. Mean concentrations of CRP by time point, treatment, and sex are presented in Table 37. There were no significant 3-way interactions (time * treatment * sex) with respect to CRP. A significant 2-way interaction (treatment * sex) was found with respect to resting concentrations of CRP ($p = 0.006$). Bonferroni post hoc testing showed that CG-F had 92% higher concentrations of CRP than PG-F ($p = 0.026$), and CG-F had 115% higher concentrations of CRP than CG-M ($p = 0.012$; Figure 8).

Table 34

Pre-Intervention Resting Concentrations of C-Reactive Protein by Sex

Pre-Intervention Variable	Males ± *SD* (n)	Females ± *SD* (n)	Overall ± *SD* (N)	*p*	Cohen's *d*
C-reactive protein (CRP) (mg/L)	1.1 ± 1.5 (22)	1.9 ± 2.1 (24)	1.5 ± 1.9 (46)	0.150	-0.432

Note. There were no significant sex differences.

Table 35

Pre-Intervention Resting Concentrations of C-Reactive Protein by Treatment

Pre-Intervention Variable	Cannabidiol Group (CG) ± *SD* (*n*)	Placebo Group (PG) ± *SD* (*n*)	Overall ± *SD* (*N*)	*p*	Cohen's *d*
C-reactive protein (CRP) (mg/L)	1.7 ± 2.1 (23)	1.3 ± 1.6 (23)	1.5 ± 1.8 (46)	0.494	0.204

Note. There were no significant treatment differences.

Table 36

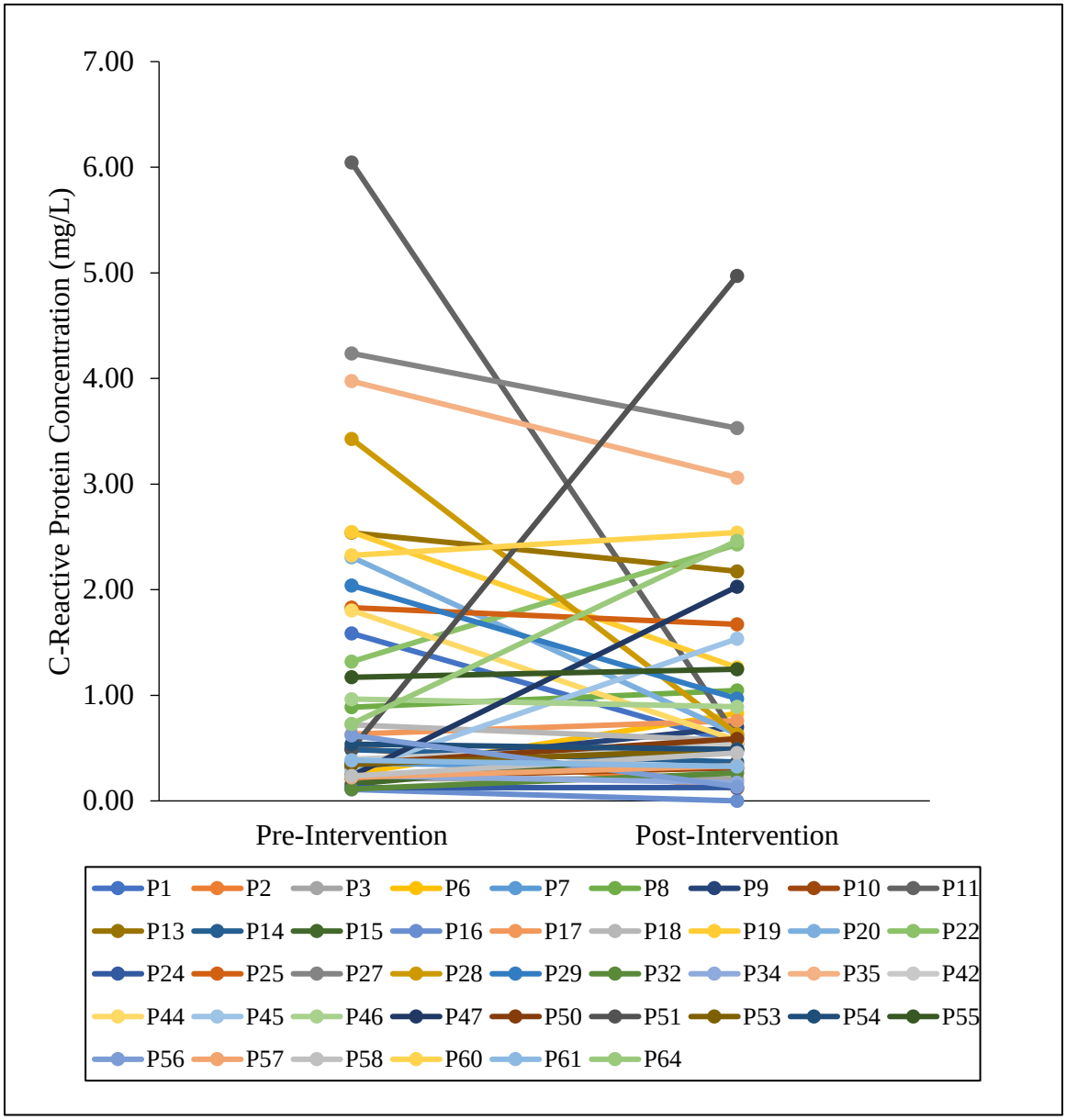
Pre-Intervention Resting Concentrations of C-Reactive Protein by Treatment and Sex

Pre-Intervention Variable	Cannabidiol Group-Male (CG-M) ± *SD* (*n*)	Cannabidiol Group-Female (CG-F) ± *SD* (*n*)	Placebo Group-Male (PG-M) ± *SD* (*n*)	Placebo Group-Female (PG-F) ± *SD* (*n*)	Overall ± *SD* (*N*)
C-reactive protein (CRP) (mg/L)	0.73 ± 0.7 (11)	2.6 ± 2.6 (12)	1.5 ± 2 (11)	1.2 ± 1.2 (12)	1.5 ± 1.9 (46)

Note. There were no significant interactions or main effects.

Figure 7

Pre- and Post-Intervention Concentrations of C-Reactive Protein



Note. P = participant number.

Table 37

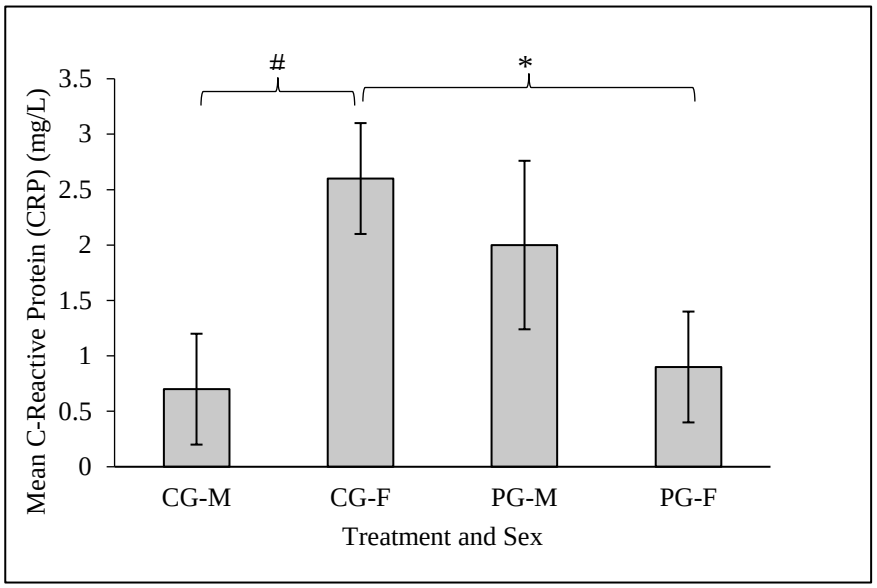
Resting Concentrations of C-Reactive Protein by Time, Treatment, and Sex

	Pre-Intervention				Post-Intervention			
Variable	Cannabidiol Group-Male (CG-M) ± *SD* (*n*)	Cannabidiol Group-Female (CG-F) ± *SD* (*n*)	Placebo Group-Male (PG-M) ± *SD* (*n*)	Placebo Group-Female (PG-F) ± *SD* (*n*)	Cannabidiol Group-Male (CG-M) ± *SD* (*n*)	Cannabidiol Group-Female (CG-F) ± *SD* (*n*)	Placebo Group-Male (PG-M) ± *SD* (*n*)	Placebo Group-Female (PG-F) ± *SD* (*n*)
C-reactive protein (CRP) (mg/L)	0.7 ± 0.7 (11)	2.6 ± 2.6 (12) [a, b]	1.5 ± 2 (11)	1.2 ± 1.2 (12	0.6 ± 0.7 (11)	2.5 ± 2.7 (12) [a, b]	2.6 ± 2.7 (11)	0.6 ± 0.5 (12)

Note. [a] Denotes overall mean CRP concentrations were significantly greater in CG-F than PG-F ($p = 0.026$) and [b] Denotes overall mean CRP concentrations were significantly greater in CG-F than CG-M ($p = 0.012$).

Figure 8

Mean C-Reactive Protein Concentrations by Treatment and Sex



Note. Data are presented as mean ± standard error (SE). CG-M = CBD male group, CG-F = CBD female group, PG-M = placebo male group, PG-F = placebo female group.

[#] Denotes overall mean CRP concentrations were significantly greater in CG-F than CG-M (p = 0.012) and [*] Denotes overall mean CRP concentrations were significantly greater in CG-F than PG-F (p = 0.026).

Resting Concentrations of Brain-Derived Neurotrophic Factor

Pre-Intervention Comparisons

Mean concentrations of brain-derived neurotrophic factor (BDNF) by sex and by treatment at the pre-intervention time point are presented in Tables 38 and 39, respectively. Overall concentrations of BDNF ranged from 5 to 87 ng/ml when all groups were combined at the pre-intervention time point. There was a significant sex difference in which females had 38% higher BDNF concentrations than males at the pre-intervention time point (p = 0.025). There were no treatment differences, no 2-way interactions (treatment assignment * sex), and no main

effects with respect to concentrations of BDNF at the pre-intervention time point. However, a medium effect size was detected in treatment $F(1, 34) = 3.504$, $p = 0.070$, $\eta^2 = 0.093$ showing that PG had 43% higher concentrations of BDNF than CG, and in sex $F(1, 34) = 3.366$, $p = 0.075$, $\eta^2 = 0.090$ showing that females had 28% higher concentrations of BDNF than males (Table 40). The inter- and intra-assay CVs for serum concentrations of BDNF were 2.5% and 5%, respectively, and both were within manufacturer ranges.

Intervention-Related Outcomes

Mean concentrations of CRP at the pre- and post-intervention time points are presented in Figure 9. Mean concentrations of BDNF by time point, treatment, and sex are presented in Table 41. There were no significant 3-way interactions (time * treatment * sex) with respect to BDNF concentrations. A significant 2-way interaction (treatment * sex) was found with respect to overall resting concentrations of BDNF ($p = 0.009$). Bonferroni post hoc testing showed overall mean BDNF concentrations in PG-F were 43% greater than CG-F ($p = 0.014$) and 39% greater than PG-M ($p = 0.008$; Figure 10).

Table 38

Pre-Intervention Resting Concentrations of Brain-Derived Neurotrophic Factor by Sex

Pre-Intervention Variable	Males ± *SD* (n)	Females ± *SD* (n)	Overall ± *SD* (N)	*p*	Cohen's *d*
Brain-derived neurotrophic factor (BDNF) (ng/mL)	28.5 ± 10 (15)	41.4 ± 20 (22)	36 ± 1.7 (37)	0.025 [a]	-0.787

Note. [a] Denotes mean BDNF concentrations in females were significantly greater than males.

Table 39

Pre-Intervention Resting Concentrations of Brain-Derived Neurotrophic Factor by Treatment

Pre-Intervention Variable	Cannabidiol Group (CG) ± *SD* (*n*)	Placebo Group (PG) ± *SD* (*n*)	Overall ± *SD* (*N*)	*p*	Cohen's *d*
Brain-derived neurotrophic factor (BDNF) (ng/mL)	31.4 ± 11 (19)	41.2 ± 22 (19)	3 ± 17.4 (38)	0.089	-0.575

Note. There were no significant treatment differences.

Table 40

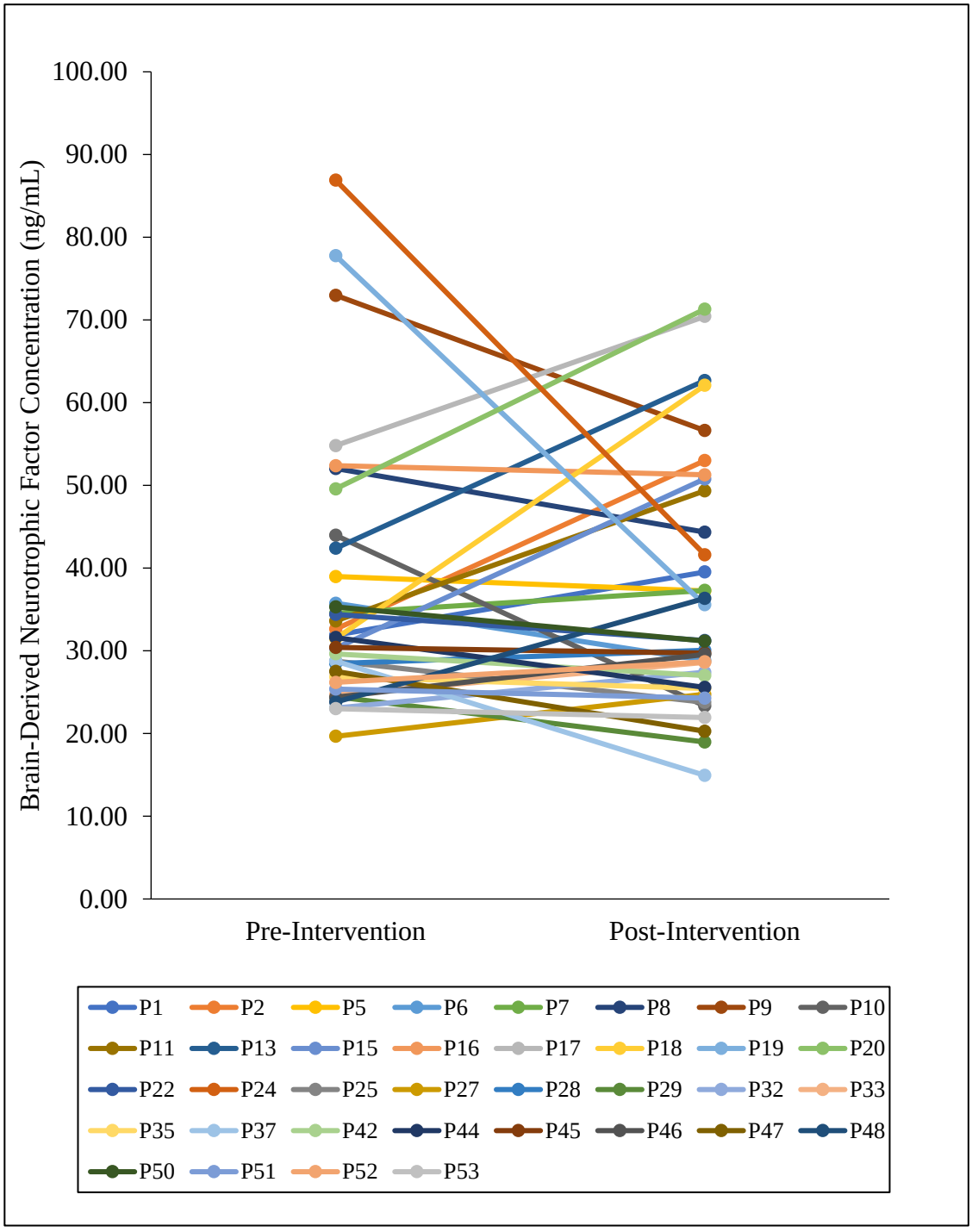
Pre-Intervention Resting Concentrations of Brain-Derived Neurotrophic Factor by Treatment and Sex

Pre-Intervention Variable	Cannabidiol Group-Male (CG-M) ± *SD* (*n*)	Cannabidiol Group-Female (CG-F) ± *SD* (*n*)	Placebo Group-Male (PG-M) ± *SD* (*n*)	Placebo Group-Female (PG-F) ± *SD* (*n*)	Overall ± *SD* (*N*)
Brain-derived neurotrophic factor (BDNF) (ng/mL)	30 ± 1.3 (8)	33 ± 0.9 (11)	33 ± 1.7 (8)	50 ± 2.4 (11)	37 ± 1.8 (38)

Note. There were no significant interactions or main effects.

Figure 9

Pre- and Post-Intervention Concentrations of Brain-Derived Neurotrophic Factor



Note. P = participant number.

Table 41

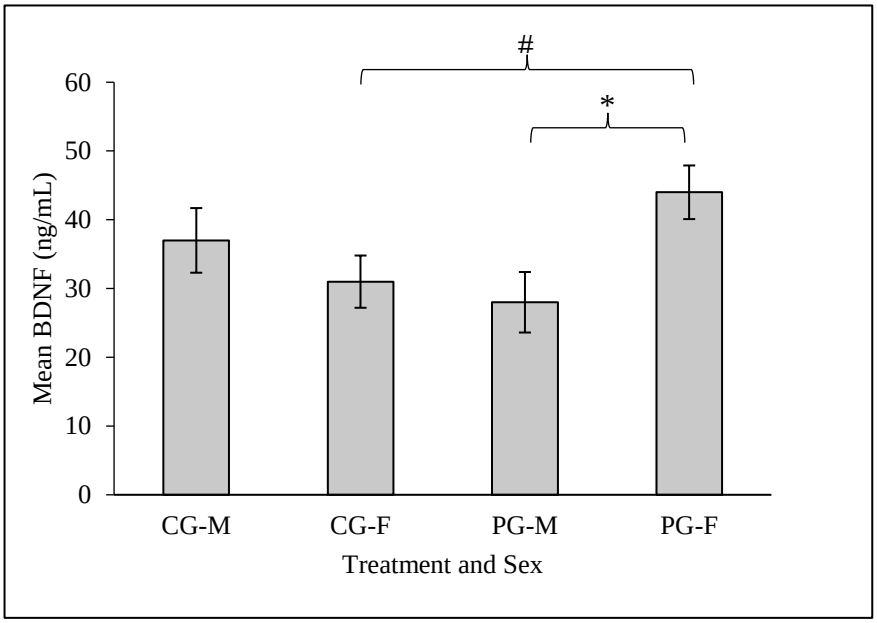
Resting Brain-Derived Neurotrophic Factor by Time, Treatment, and Sex

	Pre-Intervention				Post-Intervention			
Variable	Cannabidiol Group-Male (CG-M) ± *SD* (*n*)	Cannabidiol Group-Female (CG-F) ± *SD* (*n*)	Placebo Group-Male (PG-M) ± *SD* (*n*)	Placebo Group-Female (PG-F) ± *SD* (*n*)	Cannabidiol Group-Male (CG-M) ± *SD* (*n*)	Cannabidiol Group-Female (CG-F) ± *SD* (*n*)	Placebo Group-Male (PG-M) ± *SD* (*n*)	Placebo Group-Female (PG-F) ± *SD* (*n*)
Brain-derived neurotrophic factor (BDNF) (ng/mL)	33 ± 9.7 (7)	32.8 ± 9.2 (11)	27 ± 3.6 (7)	46.3 ± 21.4 (10) [a, b]	41.8 ± 14.2 (7)	30.2 ± 9.8 (10)	29.7 ± 9.2 (7)	42.5 ± 19.2 (10) [a, b]

Note. [a] Denotes overall mean BDNF concentrations in PG-F were significantly greater than CG-F ($p = 0.014$) and [b] Denotes overall mean BDNF concentrations in PG-F were significantly greater than PG-M ($p = 0.008$).

Figure 10

Mean Brain-Derived Neurotrophic Factor Concentrations by Treatment and Sex



Note. Data are presented as mean ± SE. BDNF = Brain-derived neurotrophic factor, CG-M = CBD male group, CG-F = CBD female group, PG-M = placebo male group, PG-F = placebo female group.

[#] Denotes overall mean BDNF concentrations in PG-F were significantly greater than CG-F (p = 0.014) and [*] Denotes overall mean BDNF concentrations in PG-F were significantly greater than PG-M (p = 0.008).

CHAPTER V

DISCUSSION

There is a great need to clarify and understand the potential health effects of long-term cannabidiol (CBD) use given false medical claims and increasing accessibility of the product to consumers. Previous research shows inconclusive results due to lack of healthy volunteers, length of CBD administration (acute vs chronic administration), imbalanced samples (unequal numbers of men and women, exclusion of women; Bhattacharyya et al., 2010; Crane, Schuster, & Gonzalez, 2013; Martin-Santos et al., 2012; Solowij et al., 2018), contamination of CBD products (presence of THC and/or heavy metals, lack of CBD purity testing; Crane, Schuster, & Gonzalez, 2013; Lisano et al., 2020; Solowij et al., 2018), and the variability of testing protocols used for determining health-related fitness (Arndt & de Wit, 2017; Babalonis et al., 2017; Haney et al., 2016). The current study was the first randomized placebo-controlled clinical trial with parallel design to explore the effects of 50 mg of daily CBD for 8 weeks in a population of healthy males and females. The main objectives of this study were to investigate overall sex or treatment assignment differences with respect to physical activity patterns, health-related fitness, mental and cognitive health before an 8-week CBD intervention and to explore whether CBD will significantly affect these outcomes. Furthermore, this study sought to explore whether CBD will significantly alter concentrations of C-reactive protein (CRP) and brain-derived neurotrophic factor (BDNF).

The first aim examined overall differences, by sex, treatment, and treatment by sex in all physical and mental health outcomes at the pre-intervention time point. With respect to sex

differences, it was specifically hypothesized that females would have lower average daily step counts and distance traveled, lower muscular strength, relative peak oxygen uptake ($\dot{V}O_2$ peak) values, and anaerobic fitness test scores, higher body fat percentage (BF%) and resting concentrations of CRP, and similar resting concentrations of BDNF, measures of psychological wellbeing (PWB), and cognitive function when compared with males at the pre-intervention time point. In the present study, there were sex differences in self-reported time spent engaged in vigorous physical activity, mean resting systolic blood pressure (RSBP) and resting diastolic blood pressure (RDBP), height, body mass (BM), lean body mass (LBM), BF%, relative $\dot{V}O_2$ peak values, bench press and back squat one repetition maximum (BP 1RM and BS 1RM, respectively) performance, absolute and relative peak and mean anaerobic power output, the purpose in life aspect of the PWB, and resting concentrations of BDNF at the pre-intervention time point. However, there were no sex differences in average daily step counts and distance traveled, cognitive function, and CRP concentrations at the pre-intervention time point.

With respect to treatment, it was specifically hypothesized that there would be no differences between males and females consuming CBD and males and females consuming placebo in all physical and mental health outcomes at the pre-intervention time point. In the present study, there was one treatment difference with respect to days spent walking in which placebo group (PG) reported 19% more days walking than CBD group (CG) at the pre-intervention time point. There were no other treatment differences in all other physical and mental health outcomes, and there were no treatment by sex interactions in all of the physical and mental health outcomes at the pre-intervention time. However, there was a main effect of sex with respect to self-reported physical activity in days spent walking, height, BM, LBM, BF%, relative $\dot{V}O_2$ peak values, BP and BS 1RM performance, absolute and relative peak and mean

anaerobic power output, the purpose of life aspect in PWB, and resting BDNF concentrations at the pre-intervention time point. Overall, there were sex differences with respect to self-reported physical activity, body size and composition, measures of cardiorespiratory fitness, muscular strength, and anaerobic fitness, PWB, and resting concentrations of BDNF, but no sex differences in average daily steps and distance traveled, cognitive function, and resting concentrations of CRP.

The final aim examined whether 8 weeks of CBD affected all physical and mental health outcomes in those consuming CBD with a hypothesis specifically stating that both males and females consuming CBD would experience increases in average daily step counts and distance traveled, improvements in relative $\dot{V}O_2$ peak, bench press and back squat 1RM performance, absolute and relative peak and mean power outputs, measures of cognitive function and PWB, reduced CRP concentrations, and increased BDNF concentrations over the course of the intervention period when compared with males and females consuming placebo. In the present study, the analyses revealed no treatment differences with respect to all physical and mental health outcomes over the course of the intervention. However, there was a significant time by treatment interaction with respect to absolute and relative peak power in which PG experienced a 9% and 3% decline in absolute and relative peak power compared with CG, which experienced no changes in either absolute or relative peak power, over the course of the intervention.

It was also hypothesized that females in the CBD group (CG-F) would experience a greater increase in average daily step counts and distance traveled, greater improvements in BF%, relative $\dot{V}O_2$ peak, measures of cognitive function and PWB, a greater reduction in CRP concentrations, and a greater increase in BDNF concentrations when compared with males in the CBD group (CG-M) over the course of the intervention. In the present study, the analyses

revealed no differences between CG-M and CG-F with respect to these physical and mental health outcomes. However, there was a significant time by sex interaction with respect to absolute and relative mean power in which females experienced a 4.5% and 3.5% decline in absolute and relative mean power compared with males, which experienced no changes in either absolute or relative mean power, over the course of the intervention. There was a main effect of sex in which males had 7% higher overall mean RSBP, 9 % higher overall mean RDBP, 18% higher overall BM, 28% higher overall LBM, 55% lower overall BF%, 40% and 22% higher overall mean peak and relative peak power (PP and RPP, respectively), and 41% and 22% higher overall mean and relative mean power (MP and RMP, respectively) than females. Interestingly, there was significant treatment by sex interaction for overall CRP concentrations in which overall mean CRP concentrations in CG-F were 92% and 115% greater than overall mean CRP concentrations in females in the placebo group (PG-F) and CG-M, respectively. Another treatment by sex interaction was also found for overall BDNF concentrations in which overall mean BDNF concentrations in PG-F were 43% and 39% greater than overall mean BDNF concentrations in CG-F and males in the placebo group (PG-M), respectively. Overall, 8 weeks of CBD supplementation did not affect physical and mental health and biomarkers of inflammation and neural health over the course of the intervention.

Resting Heart Rate and Blood Pressure

At the pre-intervention time point, mean RHR, RSBP, and RDBP were all within normal ranges when all groups were combined (N = 47; RHR: 67.4 ± 9.6 bpm, RSBP: 118 ± 10.3 mmHg, RDBP: 75.1 ± 8). There were no sex differences in RHR which was somewhat surprising as females typically have smaller hearts and left ventricular size which are often linked to higher heart rates when compared with males (Wingate, 1997). At the pre-intervention time point and

when all males were grouped together, their average blood pressure (RSBP: 121.5 ± 9.5 mmHg; RDBP: 77.7 ± 6.9 mmHg) placed them in the elevated risk category (120-129 mmHg and less than 80 mmHg) as defined by the American Heart Association (Vaduganathan et al., 2018). When all females were grouped together, their average blood pressure (RSBP: 114.9 ± 10.1 mmHg; RDBP: 72.8 ± 8.2 mmHg) placed them in the normal category (less than 120 SBP and less than 80 mmHg DBP; Vaduganathan et al., 2018). Although these sex differences in RSBP and RDBP were observed at the pre-intervention time point, no differences were found as a result of the intervention. There was a significant time by treatment interaction ($p = 0.047$), but the multiple comparisons failed to identify which time points and treatments were different. When RHR, RSBP, and RDBP were compared between treatments, there were no differences between CG and PG. Overall, these findings suggest that 8 weeks of daily, low dose CBD does not have long-term effects on RHR, RSBP, and RDBP in males and females.

The lack of a CBD-mediated change in RHR, RSBP, and RDBP is supported by a few other related studies using healthy volunteers. One study found no differences between oral CBD (600 mg) and placebo with respect to RHR after three, separate administrations over the course of a one-month time frame in healthy men. This study concluded that oral CBD was not associated with an increase in RHR (Martin-Santos et al., 2012). Another study revealed no changes in RHR, RSBP, and RDBP after 7 days of vaporized CBD inhalation (13.75 mg) in cannabis-using (using < 2 times per week) males ($n = 21$) and females ($n = 19$; Arkell et al., 2022). In one randomized placebo-controlled, double blind study with parallel design exploring the effects of oral CBD (600 mg) on hemodynamics in healthy males ($n = 13$), CBD acutely reduced resting mean arterial pressure (-2 mmHg), but did not alter RSBP and RDBP after 7 consecutive days of consumption (Sultan et al., 2020). However, when both groups completed a

3-minute isometric handgrip exercise on day 1 and 7, oral CBD attenuated increases in RSBP (-6 to -5.7 mmHg) within 2-3 minutes of acute CBD ingestion on day 1, and repeated oral CBD attenuated increases in RSBP (-8mmHg) within 1 minute of finishing the handgrip exercise on day 7, suggesting that CBD may only act on RSBP in response to acute stress (Sultan et al., 2020). These results are fascinating because mean arterial pressure is calculated as the sum of systolic blood pressure and 2 times diastolic blood pressure, and in the current study, there were no significant group differences with respect to RDBP although a medium effect size ($p = 0.070$, $\eta^2 = 0.078$) was observed at a confidence interval of 95% [-.32, 7.77]. It is important to note that the results of the present study and those of the aforementioned projects provide a glimpse into the potential effects of cannabis compounds and CBD on RHR, RSBP, RDBP, but this area is still largely unexplored.

Physical Activity Patterns

Self-reported physical activity within the last 7 days revealed that participants were below the recommendations set forth by the American College of Sports Medicine (ACSM) and the American Heart Association for physical activity guidelines for moderate intensity aerobic physical activity which is at least 30 minutes for 5 days per week (150 minutes per week) (Haskell et al., 2007). However, mean responses placed participants within guidelines for vigorous intensity aerobic physical activity which is at least 20 minutes for 3 days per week (60 mins per week; Haskell et al., 2007). Compared to these guidelines, participants engaged in 92% less and 2% more moderate and vigorous intensity aerobic physical activity (53.3 ± 36.1 minutes, 61.2 ± 44.8 minutes), respectively. Though participants did not meet the moderate intensity aerobic physical activity guidelines, they fit within the national average in which 53.3%

of adults ages 18 years and older meet the total physical activity guidelines (Centers for Disease Control, 2022).

When comparing sex, time spent engaged in moderate physical activity was not different between males and females; however, males engaged in 45% more vigorous physical activity (74 ± 47.5 minutes) than females (47.8 ± 38.4 minutes; $p = 0.044$), and females spent 24% more days walking than males ($p = 0.001$). These findings are similar to a study evaluating gender differences in physical activity and sedentary behavior using the IPAQ from 2002 to 2009 which found that males engaged in more vigorous physical activity than females from 2002-2009 ($p < 0.05$), males had significantly higher moderate physical activity than females in 2003-2004 ($p = 0.001$) and females had higher moderate physical activity than males in 2005-2006 ($p = 0.03$), and females spent significantly more time walking than males in 2002, and 2005-2006 ($p < 0.001$ and $p = 0.005$, respectively; Dagmar et al., 2011). It is important to note that self-reported physical activity was collected only at the pre-intervention time point to determine subject health status and whether the subject had the potential to exercise safely.

The Fitbit wrist accelerometer was used at both pre– and post-intervention time points to provide a more objective measure of physical activity. It is well established that individuals tend to underestimate sedentary time (time spent sitting) and overestimate moderate to vigorous physical activity (MVPA). In one study that compared IPAQ responses to Actigraph accelerometry data collected in 1,751 adults ages 19 years and older, results showed that males underestimated sedentary time (131 minutes lower) and overestimated MVPA when compared with accelerometer data (Dyrstad et al., 2014), and that this overestimation of MVPA resulted in incorrect sex differences of MVPA which suggested males engaged in 47% more MVPA when compared with females (Dyrstad et al., 2014). However, researchers concluded that IPAQ

responses may not accurately reflect physical activity and that more objective measures of physical activity should be used (Dyrstad et al., 2014). Although participants in the current study may have incorrectly reported moderate aerobic physical activity on the IPAQ, they compared favorably to national averages of accelerometry data. Mean steps per day was 9,676 in a sample of 3,744 Americans ages 20 years and older (Tudor-Locke et al., 2009) which is 17% lower than the 7-day average from participants in the present study (11,495 ± 4,193 steps per day), placing them in the active category (10,000 to 12,499 steps per day; Tudor-Locke & Bassett, 2004). Additionally, one study determined that an average of 8,000 steps per day translated to an average of 30 minutes of MVPA per day in a sample of 3,523 healthy adult males (n = 1,782) and females (n = 1,742) ages 20 and older who wore an Actigraph accelerometer for one full day (Tudor-Locke et al., 2011). By this definition, the participants in the present study met the 150-minute requirement of moderate aerobic physical activity due to their 7-day average of mean steps per day.

To date, there are no studies examining the effect of daily CBD use and physical activity using accelerometry. In the current study, no differences between CG and PG with respect to accelerometer-based steps per day and distance traveled at both the pre- and post-intervention time points were observed. However, the IPAQ revealed that PG reported spending 19% more days walking than CG (p <0.0001) at the pre-intervention time point. It is possible that the variability in days spent walking between groups may be due to poor subjective perceptions of physical activity which is a highlighted limitation of the IPAQ (Sember et al., 2020). There are also no studies which have explored the potential for CBD-related sex differences in physical activity. One recent cross-sectional study of 387 CBD-using adult males (n = 150) and females (n = 237) found that most users were female (61%). Additionally, the same study found that a

disproportionate number of users consumed CBD for post-workout muscle soreness (14% males, 7% females), general health and wellbeing (47% males, 31% females), and self-perceived anxiety (48% females, 34% males; Moltke & Hindocha, 2021). These results imply that in a sample of CBD users, only some individuals may be physically active and may be taking CBD as a post-workout recovery aid. Despite these findings and other cross-sectional studies describing CBD users (Corroon & Phillips, 2018; Fedorova et al., 2021; Wheeler, Merten, et al., 2020), it is surprising that there are no longitudinal studies to date which explore physical activity in CBD users with accelerometry.

Body Size and Composition Measures

At the pre-intervention time point, there were sex differences with respect to height, BM, LBM, and BF%, but no sex differences in BMI. Males were 7.6% taller than females (p = <0.001), 16.5% heavier than females ($p < 0.001$), had 32% more LBM than females (p = <0.001), and had 53% less BF% than females ($p < 0.001$). Although males and females did not differ with respect to BMI at the pre-intervention time point, overall mean BMI of participants was 24.8 kg/m^2 and categorized participants in the upper tier of "normal or healthy" (18.5 to 24.9 kg/m^2) according to ACSM BMI standards (D. Riebe et al., 2018). Overall male and female BMI ranged from 20 to 33 kg/m^2 and 19.6 to 30 kg/m^2, respectively, which reveals a large variance within both sexes (11 and 9, respectively). In total, 14 individuals were in the "overweight" category (25 to 29.9 kg/m^2), and 4 individuals were in the "obese" category (greater than 30 kg/m^2). However, it is important to note that BMI does not account for age, sex, bone structure, fat distribution and LBM. When comparing mean BF% at the pre-intervention time point to ACSM body composition norms, males in the current study were within the 50th to 40th percentiles, categorizing them as "average" and "slightly below average," and females were

within the 30th to 20th percentiles for BF%, categorizing them as “below average.” There were no treatment-related differences observed with respect to any of the outcome variables in this study.

There were no time by treatment by sex interactions with respect to all body size and composition outcomes. However, a main effect of sex showed that similar sex differences in BM, LBM, and BF% were still present at the end of the intervention. This suggests that 8 weeks of daily, low dose CBD may not alter body composition, regardless of sex, in an otherwise healthy, non-clinical population. The lack of CBD-related change in mean LBM is supported by one randomized, placebo-controlled, double blind study with parallel design in overweight males (n = 65) in which 6 weeks of 60 mg/d of CBD hemp oil extract (15 mg of hemp-derived CBD) resulted in no changes in LBM and fat free mass when compared with the placebo group (Lopez et al., 2020). However, another randomized study with a crossover design investigating CBD pharmacokinetics found that the time it took for CBD (30 mg) to reach maximum concentration after of acute ingestion in healthy men (n = 9) and women (n = 6) was significantly dependent on fat free mass (Williams et al., 2021). These studies suggested that, although CBD may not alter LBM, its absorption was affected by LBM and it was possible that larger doses of CBD were needed in order to observe an effect on LBM.

Interestingly, no changes in BF% were observed after 8 weeks of CBD. Other preclinical and cell culture studies suggested that CBD increased BF% through increased feeding patterns (Farrimond et al., 2012) and may decrease BF% through increasing metabolism in white adipocytes (Parray & Yun, 2016). However, these findings were not confirmed in clinical trials. In fact, the closest human studies were survey based. Results from 2 national surveys in adults 18 and over (n = 50,000) revealed that prevalence of obesity was 14% to 17% lower in cannabis users who used cannabis at least 3 days per week compared to 22% to 25% of nonusers (Le Strat

& Le Foll, 2011) suggesting that cannabinoids and their derivatives may affect body composition. It is important to note that the CBD content of the products that these individuals used was not specified. This made it difficult to determine whether changes in BF% were associated with tetrahydrocannabinol (THC), CBD, or a combination of both.

Cardiorespiratory Fitness

At the pre-intervention point, there were sex differences, but no treatment differences with respect to any of the outcome variables in the present study. Overall, males had higher mean, relative $\dot{V}O_2$ peak values than females. According to ACSM $\dot{V}O_2$ max standards, mean, relative $\dot{V}O_2$ peak values placed males in the "good" category (44.3 to 48.2 ml/kg/min) for men 20 to 29 years old and mean, relative $\dot{V}O_2$ peak values placed females in the "good" category (36.8 to 41.0 ml/kg/min) for women 20 to 29 years old (D. Riebe et al., 2018). Mean, relative $\dot{V}O_2$ peak values are not the same as true $\dot{V}O_2$ max due to the specific criteria that must be met; however, these values provide a good evaluation of the cardiorespiratory fitness in all study participants. It is important to note that $\dot{V}O_2$ peak was reported because all study participants did not reach the appropriate criteria for a $\dot{V}O_2$ max. More specifically, because this study was focused on capturing the effects of CBD in a healthy, non-elite, recreationally active population, and one that is representative of surveyed CBD users, the need to use the term $\dot{V}O_2$ peak, instead of $\dot{V}O_2$ max, was not unexpected (BrightfieldGroup, 2017; Corroon & Phillips, 2018; Fedorova et al., 2021; Wheeler, Merten, et al., 2020).

There were no $\dot{V}O_2$ peak-related time by treatment by sex interactions in this study. However, there was a main effect of time where overall relative $\dot{V}O_2$ peak values decreased by 4% ($p = 0.035$) over the course of the intervention. This decrease in $\dot{V}O_2$ peak may be attributed to the fact that data were collected during the COVID pandemic and participants were more

stressed and may have been more likely to change their dietary habits. Also, there were no significant differences in $\dot{V}O_2$ peak between treatments to suggest that CG was significantly different than PG. Currently, no other study has evaluated effects of longer term, low dose, CBD on $\dot{V}O_2$ in similar populations. However, the findings from the present study are contrary to one recent randomized, double-blind pilot study that evaluated the effects of an acute oral CBD (300 mg) dose on aerobic performance in endurance-trained men (n = 9) on two, separate occasions (Sahinovic et al., 2022). Researchers found that acute administration of CBD increased $\dot{V}O_2$ max (+ 0.1 ± 0.2 L/min) without increasing heart rate or rate of perceived exertion, leading the authors to speculate that a high dose of CBD taken just before aerobic activity may increase tissue vasodilation (Sahinovic et al., 2022). Although the aforementioned pilot study assessed the acute effects of a high dose, it also suggests that CBD may enhance aerobic performance. Other similar studies are more focused on exploring chronic cannabis consumption on $\dot{V}O_2$ max performance (Lisano et al., 2018, 2019), and cannabis administration before a $\dot{V}O_2$ test (Avakian et al., 1979; Renaud & Cormier, 1986). Despite these intriguing findings, more research which addresses the effects of both acute and long-term CBD treatments on $\dot{V}O_2$ max and cardiorespiratory fitness are needed in the future.

Muscular Strength Measures

At the pre-intervention time point, there were sex differences in BP and BS 1RM and no treatment differences. Generally, males had higher BP and BS 1RM values when compared to females. When considering relative strength, males lifted, on average, 1.2-times their bodyweight for BP and 1.4-times their bodyweight for BS, while females lifted, on average, 0.6-times their bodyweight for BP and 1-times their bodyweight for BS. Compared to other healthy and recreationally-trained males (n = 15) and females (n = 15; Seo et al., 2012), the males in the

present study had 3% lower BP 1RM values and 2.5% higher BS 1RM values, and the females in the present study had 5% higher BP 1RM values and 30% higher BS 1RM values. Given these findings, it was clear that the males and females in this study were similar and, even slightly stronger than other recreationally active males and the females.

No differences were found with respect to measures of muscular strength between CG and PG as the result of the intervention, and there was no time by treatment by sex interaction. The findings of the present study are in agreement with a recent randomized, placebo-controlled, double-blind study with crossover design that found no effect of acute oral CBD (150 mg) on maximal voluntary isomeric contraction after a damaging eccentric protocol in the elbow flexors of untrained males (n = 13; Cochrane-Snyman et al., 2021). While the findings from the present study are interesting, this general area of inquiry is confounded by the type of strength measure, acute vs. chronic CBD administration, and a lack of female study participants.

In the current study, CG-M and CG-F did not experience significant changes in both bench press and back squat 1RMs. Though these increases were not statistically significant, CG-M experienced a 1% and 2.6% increase in bench press and back squat 1RM values, respectively and CG-F experienced a 2.5% and 8% increase in bench press and back squat 1RM values, respectively. Given these responses, it is plausible that CBD may be acting on downstream targets in a manner that preserves skeletal muscle with chronic resistance training. This idea was observed in one preclinical study (Langer et al., 2021), and is supported by one human study examining changes in concentrations of creatine kinase and myoglobin (Isenmann et al., 2021). However, it is important to note that biological sex may play a role in this response. In the current study, PG-M experienced a 2% and 5% increase in both BP and BS 1RM, respectively, and PG-F experienced a 1.2% decrease in bench press 1RM and 4% increase in back squat 1RM,

and these changes were not significantly different from CG-M and CG-F. A main effect of time was also observed in which back squat 1RM values for all groups increased by 5.4% by the post-intervention time point. Thus, it is unknown whether molecular targets of CBD are only stimulated during strenuous training sessions and whether biological sex plays a role in this response.

It is also unknown whether the CBD response, if any, to strenuous resistance training is similar in all skeletal muscle fiber types in both sexes. The current study found a main effect of sex on both strength measures, but no time by treatment by sex interactions, suggesting that sex influences upper and lower body strength measures regardless of long-term CBD use. Sex differences are documented in animal studies. One study showed that after an acute bout of eccentric exercise, female rats had less pronounced skeletal muscle fiber damage compared with male rats (Komulainen et al., 1999), and after a unilateral hindlimb muscle injury exercise, female mice experienced less leukocyte activation into damaged myofibers compared with males (St. Pierre Schneider et al., 1999). Human research also shows less leukocyte invasion after acute damaging eccentric exercise in females compared with males (Stupka et al., 2000). Thus, more research focused on understanding how CBD might influence the sex-related differences in strength measures and muscle physiology are necessary.

Anaerobic Fitness Measures

At the pre-intervention time point, all anerobic power outputs except anaerobic fatigue (AF) were significantly different between males and females and no differences in treatment were found. Sex differences in anaerobic fitness are typical in previous and current normative data (Borgert-Poepping et al., 2008; Maud & Shultz, 1986). Compared to previous normative data, male and female mean PP placed both groups in the 85-90th percentile (Above Average),

MP in the 60-70th percentile (Average), RPP placed both in the 60-70th percentile (Average), RMP placed males in the 60-80th percentile (Average) and females in the 5-10th percentile (Well Below Average), and AF placed both groups in the 5-10th percentile (Well Below Average; Maud & Shultz, 1986) Compared with updated normative data from other college-age individuals (unspecified number of participants per sex), males and females in the current study had 5% lower PP and 7.8% higher PP, respectively (Borgert-Poepping et al., 2008). Compared with 18–25-year-old intercollegiate athletes, males and females in the current study had 16% and 9% lower PP, 18% and 14% lower MP, 15% and 16% lower RPP, and 17% and 21% lower RMP, respectively (Zupan et al., 2009). This classified male mean PP as "below average," MP as "below average," RPP as "below average" and RMP as "poor" (Zupan et al., 2009). This also classified female mean PP as "below average," MP as "below average," RPP as "below average," and RMP as "poor" (Zupan et al., 2009). The AF for the males and females in the present study placed them in the 5th percentile (Well Below Average; Maud & Shultz, 1986).

Mean PP, RPP, MP, RMP, and AF in CG and PG did not significantly change over the course of the intervention period, and there were no time by treatment by sex interactions. However, a time by treatment effect was found in which PG experienced a 9% decrease in mean PP ($p = 0.006$) and a 3% decrease in mean RPP compared to CG ($p = 0.006$). After 8 weeks, CG experienced a 2.5% increase in mean PP whereas PG experienced a 9% decrease in mean PP. These translated to a 2% and 2.5% increase in mean RPP for CG-M and CG-F, but a 9% and 10% decrease in mean RPP for PG-M and PG-F, respectively. Participants were instructed to maintain their physical activity and the accelerometry data from this study supports this claim. These results suggest that it is possible for long-term CBD supplementation to attenuate decreases in peak anaerobic power over time.

A time by sex effect was also found in which females experienced a 4.5% decrease in mean MP ($p = 0.021$) and a 3.5% decrease in mean RMP compared to males ($p = 0.018$). With respect to mean MP, CG and PG experienced a 0.2% and 10% decrease in MP over the course of the intervention, respectively; however, these changes were not significant. Within CG, mean MP changes over time were different for males and females. In fact, CG-M and CG-F experienced a 2% and 4% increase in mean MP, respectively, and these increases translated to a 1.4% increase in mean RMP for CG-M, but a 12% decrease in mean RMP for CG-F over the course of the intervention. Within PG, PG-M experienced a 1% increase in mean MP and PG-F experienced a 7% decrease in mean MP and these changes translated to no change in mean RMP for PG-M, but a 7% decrease in mean RMP for PG-F, respectively. In summary, females experienced a significant decrease in MP by the end of the study, regardless of CBD use. Additionally, a medium effect size of time for AF% was observed ($p = 0.067$, $\eta^2 = 0.078$) at 95% [-1, .09], but no other large, main effects of time were found.

The intervention suggests that the effect of CBD on mean PP and the influence of sex on mean MP may depend on the duration of the intervention. It is plausible that long-term CBD supplementation may not impair anaerobic power output but rather, act to maintain anaerobic power output during times of stress. These results also suggest that males and females may respond differently to anaerobic testing over time and this response may be influenced by long-term CBD supplementation. This is the first study to explore the effect of chronic, low dose CBD over the course of 8 weeks on anerobic power output and there is currently no literature to use for comparison.

Mental Health and Cognition Surveys

Given the gender gap in mental health (Green et al., 2019; Riecher-Rössler, 2017; Terlizzi & Norris, 2021) and the potential of CBD to affect mental health and wellbeing, scores were obtained at both pre-intervention and post-intervention time points to determine mental health status with a specific focus on eudaimonic wellbeing which refers to self-recognition as the full functioning of the person (Di Fabio & Palazzeschi, 2015). At the pre-intervention time point, there were no treatment differences. However, sex differences were observed in one of the 6 aspects of PWB at the pre-intervention time point in which females had higher scores in purpose for life aspect when compared with males. No significant differences were found with respect to all other aspects of the PWB scale at the pre-intervention time point. These findings are similar to one study that found gender differences in Filipino, college-age males (n = 110) and females (n = 478) in which females had a significantly higher purpose in life scores than males ($p < 0.001$; Perez, 2012). The findings in the current study are also similar to another investigation of Westernized college-age males (n = 40) and females (n = 91) and found that females also had significantly higher purpose in life scores score than males ($p = 0.002$; Ludban & Gitimu, 2015).

No sex or treatment differences with respect to cognitive function and cognitive function abilities T scores were found at the pre-intervention time point. These findings are similar to others that have compared cognitive function in normal, general populations. The mean cognitive function T score categorizes participants from the current study as typical (T score range from 25-75), with males 3% below the male T score mean, and females 1% above the female mean in a sample of healthy males (n = 493) and females (n = 516) without neuropsychiatric disorders (Iverson et al., 2021). Cognitive function abilities T scores were similar to another study that

found no gender differences in healthy controls that were compared with a medical outpatient population (Saffer et al., 2015). Mean cognitive function abilities T scores from participants in this study were 1.8% and 2% lower than those healthy, non-depressed adult controls (n = 134) and non-anxious adult controls (n = 130; Saffer et al., 2015).

No time by treatment by sex interactions were found for all 6 aspects of the PWB aspects and both cognitive scale T scores. However, there was main effect of time on three of the six PWB aspects. Mean personal growth, positive relation with others, purpose in life scores in significantly decreased by 5%, 7%, and 7% over the course of the intervention ($p < 0.001$, $p = 0.017$, and $p = 0.016$, respectively). A main effect of sex was also found with respect to mean purpose in life scores in which females had 11.7% overall higher scores than males ($p = 0.008$). This finding could be attributed to timing of data collection which began January 2021 and ended March 2022. Decreased PWB and potentially overall retention and attrition rates may have been impacted by local (campus and community) and global events during this 17-month period of data collection. These events included economic and financial consequences from the coronavirus-19 pandemic, and major social and cultural events such as a controversial presidential election, the Tokyo Summer Olympics, and the Russia-Ukraine War. Other researchers agree that these types of disruptions significantly altered mental health and wellbeing (Moreno et al., 2020; Pfefferbaum & North, 2020).

It was hypothesized that positive changes in PWB and cognition would be observed from long-term CBD use in this study due to evidence highlighting its protective effects against induced psychosis (Bhattacharyya et al., 2010; Bloomfield et al., 2020) and anxiety (Crippa et al., 2004). Compared to these previous acute CBD models in healthy men completing MRI analyses and cognitive function tasks, the current study results suggest that CBD may not

provide improvements or a resistance to decrements in cognition. Animal research already demonstrates that acute and chronic CBD administration improves measures of cognitive function and mental health (Barichello et al., 2012; Campos et al., 2015; Mori et al., 2017; Osborne, Solowij, Babic, et al., 2017; Sales et al., 2020; Schiavon et al., 2016). This finding has yet to be consistently shown in the literature. It is also necessary to include females in these studies. In fact, other studies have found that men and women perform cognitive tasks differently after consuming acute oral and vaporized CBD (Schoedel et al., 2018; Spindle et al., 2020).

Biomarkers of Inflammation and Neural Health

There were no sex differences in concentrations of CRP at the pre-intervention time point, and no interactions or main effects of time, treatment, or sex in the 3-way mixed ANOVA. Mean concentrations of CRP for total participants were 18% lower than concentrations of CRP of other healthy and active individuals (males: n = 405, females: n = 454) ages 25-75 years old (Pischon et al., 2003). When biological sex was taken into account, males and females in the current study had 53% and 9% lower concentrations of CRP compared to healthy men and women, respectively (Pischon et al., 2003). According to the CVD risk stratification literature (Lee et al., 2019; Ridker, 2003), individual CRP concentrations at the pre-intervention time point placed half of the participants in the present study (50%; males: n = 16, females: n = 12) in the low-risk category (serum CRP < 1 mg/L) for cardiovascular disease (CVD), while individual CRP values placed almost 24% of participants in the present study (22% males: n = 4 , females: n = 7) in the moderate-risk category for CVD (serum CRP 1-3 mg/L). Only a few (15%, males: n = 2, females: n = 5) CRP values placed individuals into the high-risk for CVD category (serum CRP >3 mg/L). Prior research shows that sex differences in concentrations of CRP are most attributed to differences in adiposity and BMI (Khera et al., 2009; Rexrode et al., 2003; Thorand

et al., 2006). An additional bivariate correlational analysis confirmed this association in the present study; concentrations of CRP were directly correlated with BF% ($r = 0.571$, $p = 0.004$), BMI ($r = 0.448$, $p = 0.018$), and BM ($r = 0.649$, $p < 0.001$) in females, but not in males. Additionally, concentrations of CRP were also inversely correlated with relative $\dot{V}O_2$ peak ($r = -0.493$, $p = 0.014$) only in females at the pre-intervention time point.

The relationship of adiposity and CRP may also explain why a treatment by sex interaction was found with respect to total concentrations of CRP in which CG-F had greater mean concentrations of serum CRP when compared to both CG-M and PG-F. It is important to note that these values are the average concentrations of CRP from both pre- and post-intervention time points and comparisons reflect the interaction of between-group factors as there were no main effect or interactions of time. Therefore, this finding suggests that the effect of 8 weeks of CBD on concentrations of serum CRP depends on whether the user is male or female. This finding complements the aforementioned CBD survey-based studies which identified females as common CBD users who may not be meeting in ACSM physical activity recommendations (BrightfieldGroup, 2017; Corroon & Phillips, 2018; Fedorova et al., 2021; Wheeler, Merten, et al., 2020). The body size and composition measurements of the females in the present study are correlated with CRP concentrations and their IPAQ responses match this profile of typical CBD users. Interestingly, two interactions (time * sex and time * treatment * sex) were observed to have a medium effect size at a 95% confidence interval (time * sex: $p = 0.086$, $\eta^2 = 0.069$; time * treatment * sex: $p = 0.086$, $\eta^2 = 0.068$); however, these interactions did not reach significance. This presents a fascinating finding and highlights the need for more research exploring chronic CBD administration on serum concentrations in CRP in males and females, as well as exploring the molecular underpinnings related to this change.

In the present study, mean concentrations of BDNF in males and females at the pre-intervention time point were all within normal ranges of reported serum concentrations of BDNF for healthy adults (8 to 46 ng/mL and 18 to 26 ng/mL; Dong et al., 2021; Elsner et al., 2020; Kallies et al., 2019; Lisano et al., 2020; Szuhany & Otto, 2020; Toll et al., 2020; Trajkovska et al., 2007). A significant sex difference was found with respect to concentrations of BDNF in which females were 38% higher than males at the pre-intervention time point (p = 0.025). This sex difference is supported in a large body of research that shows that circulating concentrations of BDNF are higher in women than in men (Collins et al., 2021; Glud et al., 2019), with others suggesting that age, body composition, and mental and cognitive health affect the degree of change between males and females (Bus et al., 2011; Dong et al., 2021; Ihara et al., 2016). However, a bivariate correlational analysis revealed that there were no significant relationships between resting concentrations of BDNF and age, BM, LBM, BF%, PWB aspects, and cognitive function scale T scores in the present study, at the pre-intervention time point, for both males and females. Overall, participants had normal, healthy ranges of resting concentrations of peripheral, serum BDNF. There were no additional treatment or treatment by sex interactions and main effects at the pre-intervention time point.

Interestingly, there was a significant treatment by sex interaction in which overall mean concentrations of BDNF in PG-F were 43% greater than CG-F (p = 0.014) and 39% greater than PG-M (p = 0.008). It is important to note that overall BDNF concentrations are the total of both pre- and post-intervention time points. Thus, this suggests that the effect of CBD may be more pronounced in females compared with males. This is an interesting finding because mean concentrations of BDNF were 28% higher in males and 13% lower in females over the course of the intervention, but these were not significant, suggesting that CBD may not maintain or

attenuate losses in concentrations of BDNF in females. However, clinical studies with psychiatric populations suggest that CBD may have therapeutic effects in females that is correlated with improvements in concentrations of BDNF (Campos et al., 2016, 2017). It is possible that during times of stress, CBD has protective properties that may be more pronounced in females. This is demonstrated in animal models showing the agonistic effects of CBD on the inhibitory G-protein coupled receptor known as 5-beta hydroxytryptamine receptor 1, resulting in antiepileptic, antidepressant, and anti-anxiolytic effects (Campos et al., 2016; Sartim et al., 2016). Although this suggests that females may experience positive changes in concentrations of BDNF with acute CBD, the current study did not observe this phenomenon and this underlying CBD mechanism is not confirmed in healthy, human females. It is possible that the concentrations of BDNF in CG-F reflect some degree of stress or mental health condition. However, there were no positive relationships with PWB aspects and concentrations of BDNF when bivariate correlational analyses were carried out by treatment and sex, and there were no indications of current psychiatric stress from the medical health questionnaire. Overall, the difference in total concentrations of BDNF between CG-F, PG-F, and PG-M present another fascinating finding which suggests that CBD may affect this neural health biomarker in both sexes differently.

Limitations and Advantages

The results of this study should be interpreted with caution due to several limitations. First and foremost, as this analysis was exploratory in nature, sample sizes were specifically powered by concentrations of CRP in individuals who underwent an exercise intervention. It was not specifically powered to detect sex differences nor differences in any other outcome. The resulting smaller sample size limits the generalizability of the study to other similar populations.

A second limitation is linked to the CBD intervention duration. This study involved 8 weeks of daily CBD ingestion in healthy individuals and is similar to other long-term studies investigating CBD responses for 4 to 6 weeks in patients with schizophrenia (200 to 1,000 mg/d; Boggs et al., 2018; Leweke et al., 2012; McGuire et al., 2018), 13 weeks in patients with type 2 diabetes and dyslipidemia (200 mg/d; Jadoon et al., 2016), 8 weeks in patients with Crohn's disease (20 mg/d; Naftali et al., 2017), and for 10 weeks in patients with ulcerative colitis (50 to 250 mg/d; Irving et al., 2018). Although the present study was similar in length to these clinical populations, it is unknown whether non-clinical populations respond in the same way. Neuropsychiatric populations also show improvements after 6-8 weeks, but with a possible need to combine additional cannabinoids for treatment of some neuropsychiatric disorders (Boggs et al., 2018; Leweke et al., 2012; McGuire et al., 2018). It is possible that the individuals in the current study adjusted to the 50 mg of CBD within the 8 weeks, and as a result, may have become desensitized or may have needed additional supplement compounds to experience changes in physical or mental health outcomes. It is also possible that the time was not long enough for CBD to be influential in the system due to low potency from low absorption rate; however, the current study had participants consume CBD (which was combined with MCT oil) after dinner to increase its bioavailability. Future plans to explore intervention lengths in healthy individuals should include assessing outcomes at more than two time points.

The final limitation to this study was CBD dose, which may have been too small to observe a change in all physical and mental health outcomes. A CBD dose of 50 mg was chosen as it more closely resembles products available to (and used by) the general population. There is a wide range of doses used in other studies depending on neurological condition with an average CBD dose ranging anywhere from 1-5 mg/kg/d to 20 mg/kg/d (Silva et al., 2020). For example,

when considering a 67 kg female and 80 kg male (mean BM of both sexes in the current study), a CBD dose of 15 mg/kg/d, which is 5 mg/kg/d less than an experimental trial of CBD in Dravet Syndrome (Devinsky et al., 2017), would be equivalent to 1,005 mg (67 kg * 15 mg/kg/d) and 1,200 mg (80 kg * 15 mg/kg/d) of CBD for each, respectively. Additionally, the BM of participants in the current study ranged from 49 to 106 kg, which would have resulted in uneven dosages from 750 mg to 1,250 mg, dosing similar to clinical trials in children and young adults that showed 20 mg/kg/d significantly reduced seizures (Devinsky et al., 2014, 2017, 2018). Although CBD has not demonstrated a potential for abuse and is well tolerated (Huestis et al., 2019; Schoedel et al., 2018), there is limited information and inconclusive findings from human pharmacokinetic studies of healthy and patient populations, males and females, and cannabis naïve participants (Cooper & Craft, 2018; Nadulski et al., 2005; Williams et al., 2021). Thus, more dose-response trials are needed in healthy, non-clinical populations to better provide support for CBD doses.

This study has a few strengths that should be noted. The results of this study add to the limited knowledge from randomized controlled trials in CBD-related research in recreationally active adult males and females. This study also provides critical knowledge for public health officials and healthcare professionals regarding the effects of CBD and its potential sex-related differences on anaerobic fitness and resting concentrations of CRP and BDNF. Lastly, this study also provides information on the effects of CBD on females, which is an important addition as many current CBD surveys show CBD users are predominantly female (Fedorova et al., 2021; Moltke & Hindocha, 2021; Wheeler, Merten, et al., 2020).

Conclusions and Future Directions

This study suggests that 8 weeks of CBD consumption does not alter body composition, cardiovascular measures, cardiorespiratory fitness, and muscular strength. However, results from this study suggest it may serve as a potential aid in preventing decreases in anerobic power output with respect to mean PP and MP, and that its effect on resting concentrations of CRP and BDNF are different between males and females.

Given the wide variety of CBD compounds, modes of delivery, and the very little that is known about the effects of CBD on the mental and physical status of otherwise healthy people, there is room for future high quality randomized, controlled clinical trials. Additionally, there is very little information about the potential for sex to influence the effects of CBD. This area of research is growing, and future funding may help support studies which expand our knowledge in the area.

REFERENCES

Abd El-Kader, S. M., & Al-Jiffri, O. H. (2019). Aerobic exercise modulates cytokine profile and sleep quality in elderly. *African Health Sciences, 19*(2), 2198-2207. https://doi.org/10.4314/ahs.v19i2.45

Abd El-Kader, S. M., & Al-Shreef, F. M. (2018). Inflammatory cytokines and immune system modulation by aerobic versus resisted exercise training for elderly. *African Health Sciences, 18*(1), 120-131. https://doi.org/10.4314/ahs.v18i1.16

Ali, E. T., Jabbar, A. S., & Mohammed, A. N. (2019). A comparative study of interleukin 6, inflammatory markers, ferritin, and hematological profile in rheumatoid arthritis patients with anemia of chronic disease and iron deficiency anemia. *Anemia, 2019,* Article 3457347. https://doi.org/10.1155/2019/3457347

Alonso, M., Medina, J. H., & Pozzo-Miller, L. (2004). Erk1/2 activation is necessary for bdnf to increase dendritic spine density in hippocampal ca1 pyramidal neurons. *Learning & Memory, 11*(2), 172-178. https://doi.org/10.1101/lm.67804

Angelucci, F., Ricci, V., Spalletta, G., Pomponi, M., Tonioni, F., Caltagirone, C., & Bria, P. (2008). Reduced serum concentrations of nerve growth factor, but not brain-derived neurotrophic factor, in chronic cannabis abusers. *European Neuropsychopharmacology: The Journal of the European College of Neuropsychopharmacology*, *18*(12), 882-887. https://doi.org/10.1016/j.euroneuro.2008.07.008

Arkell, T. R., Kevin, R. C., Vinckenbosch, F., Lintzeris, N., Theunissen, E., Ramaekers, J. G., & McGregor, I. S. (2022). Sex differences in acute cannabis effects revisited: Results from two randomized, controlled trials. *Addiction Biology*, *27*(2), e13125. https://doi.org/10.1111/adb.13125

Arndt, D. L., & de Wit, H. (2017). Cannabidiol does not dampen responses to emotional stimuli in healthy adults. *Cannabis Cannabinoid Res*, *2*(1), 105-113. https://doi.org/10.1089/can.2017.0014

Ativie, F., Komorowska, J. A., Beins, E., Albayram, Ö., Zimmer, T., Zimmer, A., Tejera, D., Heneka, M., & Bilkei-Gorzo, A. (2018). Cannabinoid 1 receptor signaling on hippocampal gabaergic neurons influences microglial activity. *Frontiers in Molecular Neuroscience*, *11*, 295. https://doi.org/10.3389/fnmol.2018.00295

Autry, A. E., Adachi, M., Cheng, P., & Monteggia, L. M. (2009). Gender-specific impact of brain-derived neurotrophic factor signaling on stress-induced depression-like behavior. *Biological Psychiatry*, *66*(1), 84-90. https://doi.org/10.1016/j.biopsych.2009.02.007

Avakian, E. V., Horvath, S. M., Michael, E. D., & Jacobs, S. (1979). Effect of marihuana on cardiorespiratory responses to submaximal exercise. *Clinical Pharmacology and Therapeutics*, *26*(6), 777-781. https://doi.org/10.1002/cpt1979266777

Babalonis, S., Haney, M., Malcolm, R. J., Lofwall, M. R., Votaw, V. R., Sparenborg, S., & Walsh, S. L. (2017). Oral cannabidiol does not produce a signal for abuse liability in frequent marijuana smokers. *Drug and Alcohol Dependence*, *172*, 9-13. https://doi.org/10.1016/j.drugalcdep.2016.11.030

Baechle, T. R., & Earle, R. W. (2008). *Essentials of strength training and conditioning* (3 ed.). Human Kinetics.

Barcellos, F. C., Del Vecchio, F. B., Reges, A., Mielke, G., Santos, I. S., Umpierre, D., Bohlke, M., & Hallal, P. C. (2018). Exercise in patients with hypertension and chronic kidney disease: A randomized controlled trial. *Journal of Human Hypertension*, *32*(6), 397-407. https://doi.org/10.1038/s41371-018-0055-0

Barichello, T., Ceretta, R. A., Generoso, J. S., Moreira, A. P., Simões, L. R., Comim, C. M., Quevedo, J., Vilela, M. C., Zuardi, A. W., Crippa, J. A., & Teixeira, A. L. (2012). Cannabidiol reduces host immune response and prevents cognitive impairments in wistar rats submitted to pneumococcal meningitis. *European Journal of Pharmacology*, *697*(1-3), 158-164. https://doi.org/10.1016/j.ejphar.2012.09.053

Bar-Or, O. (1987). The wingate anaerobic test. An update on methodology, reliability and validity. *Sports Medicine*, *4*(6), 381-394. https://doi.org/10.2165/00007256-198704060-00001

Beavers, K. M., Hsu, F. C., Isom, S., Kritchevsky, S. B., Church, T., Goodpaster, B., Pahor, M., & Nicklas, B. J. (2010). Long-term physical activity and inflammatory biomarkers in older adults. *Medicine and Science in Sports and Exercise*, *42*(12), 2189-2196. https://doi.org/10.1249/MSS.0b013e3181e3ac80

Beltz, N. M., Gibson, A. L., Janot, J. M., Kravitz, L., Mermier, C. M., & Dalleck, L. C. (2016). Graded exercise testing protocols for the determination of vo(2)max: Historical perspectives, progress, and future considerations. *Journal of Sports Medicine*, *2016*, Article 3968393. https://doi.org/10.1155/2016/3968393

Bergamaschi, M. M., Queiroz, R. H. C., Chagas, M. H. N., De Oliveira, D. C. G., De Martinis, B. S., Kapczinski, F., Quevedo, J., Roesler, R., Schröder, N., & Nardi, A. E. (2011). Cannabidiol reduces the anxiety induced by simulated public speaking in treatment-naive social phobia patients. *Neuropsychopharmacology*, *36*(6), 1219-1226. https://doi.org/10.1038/npp.2011.6

Bermudez, E. A., Rifai, N., Buring, J., Manson, J. E., & Ridker, P. M. (2002). Interrelationships among circulating interleukin-6, c-reactive protein, and traditional cardiovascular risk factors in women. *Arteriosclerosis, Thrombosis, and Vascular Biology*, *22*(10), 1668-1673. https://doi.org/10.1161/01.atv.0000029781.31325.66

Bhattacharyya, S., Morrison, P. D., Fusar-Poli, P., Martin-Santos, R., Borgwardt, S., Winton-Brown, T., Nosarti, C., O'Carroll, C. M., Seal, M., & Allen, P. (2010). Opposite effects of δ-9-tetrahydrocannabinol and cannabidiol on human brain function and psychopathology. *Neuropsychopharmacology*, *35*(3), 764-774. https://doi.org/10.1038/npp.2009.184

Bhattacharyya, S., Wilson, R., Appiah-Kusi, E., O'Neill, A., Brammer, M., Perez, J., Murray, R., Allen, P., Bossong, M. G., & McGuire, P. (2018). Effect of cannabidiol on medial temporal, midbrain, and striatal dysfunction in people at clinical high risk of psychosis: A randomized clinical trial. *JAMA Psychiatry*, *75*(11), 1107-1117. https://doi.org/10.1001/jamapsychiatry.2018.2309

Bidwell, A. J., Fairchild, T. J., Redmond, J., Wang, L., Keslacy, S., & Kanaley, J. A. (2014). Physical activity offsets the negative effects of a high-fructose diet. *Medicine and Science in Sports and Exercise*, *46*(11), 2091-2098. https://doi.org/10.1249/mss.0000000000000343

Bilbo, S. D., Smith, S. H., & Schwarz, J. M. (2012). A lifespan approach to neuroinflammatory and cognitive disorders: A critical role for glia. *Journal of Neuroimmune Pharmacology*, *7*(1), 24-41. https://doi.org/10.1007/s11481-011-9299-y

Bisogno, T., Hanus, L., De Petrocellis, L., Tchilibon, S., Ponde, D. E., Brandi, I., Moriello, A. S., Davis, J. B., Mechoulam, R., & Di Marzo, V. (2001). Molecular targets for cannabidiol and its synthetic analogues: Effect on vanilloid vr1 receptors and on the cellular uptake and enzymatic hydrolysis of anandamide. *Br J Pharmacol*, *134*(4), 845-852. https://doi.org/10.1038/sj.bjp.0704327

Bloomfield, M. A., Green, S. F., Hindocha, C., Yamamori, Y., Yim, J. L. L., Jones, A. P., Walker, H. R., Tokarczuk, P., Statton, B., & Howes, O. D. (2020). The effects of acute cannabidiol on cerebral blood flow and its relationship to memory: An arterial spin labelling magnetic resonance imaging study. *Journal of Psychopharmacology*, *34*(9), 981-989. https://doi.org/10.1177/0269881120936419

Boggs, D. L., Surti, T., Gupta, A., Gupta, S., Niciu, M., Pittman, B., Schnakenberg Martin, A. M., Thurnauer, H., Davies, A., D'Souza, D. C., & Ranganathan, M. (2018). The effects of cannabidiol (cbd) on cognition and symptoms in outpatients with chronic schizophrenia a randomized placebo controlled trial. *Psychopharmacology*, *235*(7), 1923-1932. https://doi.org/10.1007/s00213-018-4885-9

Bollinger, J. L., Bergeon Burns, C. M., & Wellman, C. L. (2016). Differential effects of stress on microglial cell activation in male and female medial prefrontal cortex. *Brain Behav Immun*, *52*, 88-97. https://doi.org/https://doi.org/10.1016/j.bbi.2015.10.003

Bonini, S. A., Premoli, M., Tambaro, S., Kumar, A., Maccarinelli, G., Memo, M., & Mastinu, A. (2018). Cannabis sativa: A comprehensive ethnopharmacological review of a medicinal plant with a long history. *Journal of Ethnopharmacology, 227,* 300-315. https://doi.org/10.1016/j.jep.2018.09.004

Borg, G. A. (1982). Psychophysical bases of perceived exertion. *Medicine and Science in Sports and Exercise, 14*(5), 377-381.

Borgert-Poepping, M., Gressick, B., & Bredle, D. (2008). *Updated wingate anaerobic power test norms*. University of Wisconsin-Eu Claire. https://minds.wisconsin.edu/bitstream/handle/1793/30629/Borgert-PoeppingSpr08.pdf?sequence=1&isAllowed=y

Borson, S., Scanlan, J. M., Chen, P., & Ganguli, M. (2003). The mini-cog as a screen for dementia: Validation in a population-based sample. *J Am Geriatr Soc*, *51*(10), 1451-1454. https://doi.org/10.1046/j.1532-5415.2003.51465.x

Boyne, P., Meyrose, C., Westover, J., Whitesel, D., Hatter, K., Reisman, D. S., Cunningham, D., Carl, D., Jansen, C., Khoury, J. C., Gerson, M., Kissela, B., & Dunning, K. (2019). Exercise intensity affects acute neurotrophic and neurophysiological responses poststroke. *Journal of Applied Physiology, 126*(2), 431-443. https://doi.org/10.1152/japplphysiol.00594.2018

Brigadski, T., & Leßmann, V. (2020). The physiology of regulated bdnf release. *Cell and Tissue Research*, *382*(1), 15-45. https://doi.org/10.1007/s00441-020-03253-2

BrightfieldGroup, H. (2017). *Understanding cannabidiol (cbd), industry expert report*. BrightfieldGroup. https://daks2k3a4ib2z.cloudfront.net/595e80a3d32ef41bfa200178/59946dd86c6b200001c5b9cb_CBD_-_HelloMD_Brightfield_Study_-_Expert_Report_-_FINAL.pdf

Briken, S., Rosenkranz, S. C., Keminer, O., Patra, S., Ketels, G., Heesen, C., Hellweg, R., Pless, O., Schulz, K.-H., & Gold, S. M. (2016). Effects of exercise on irisin, bdnf and il-6 serum levels in patients with progressive multiple sclerosis. *Journal of Neuroimmunology, 299*, 53-58. https://doi.org/10.1016/j.jneuroim.2016.08.007

Britch, S. C., Goodman, A. G., Wiley, J. L., Pondelick, A. M., & Craft, R. M. (2020). Antinociceptive and immune effects of delta-9-tetrahydrocannabinol or cannabidiol in male versus female rats with persistent inflammatory pain. *The Journal of Pharmacology and Experimental Therapeutics, 373*(3), 416-428. https://doi.org/10.1124/jpet.119.263319

Britch, S. C., Wiley, J. L., Yu, Z., Clowers, B. H., & Craft, R. M. (2017). Cannabidiol-delta(9)-tetrahydrocannabinol interactions on acute pain and locomotor activity. *Drug and Alcohol Dependence, 175*, 187-197. https://doi.org/10.1016/j.drugalcdep.2017.01.046

Bus, B. A., Molendijk, M. L., Penninx, B. J., Buitelaar, J. K., Kenis, G., Prickaerts, J., Elzinga, B. M., & Voshaar, R. C. (2011). Determinants of serum brain-derived neurotrophic factor. *Psychoneuroendocrinology, 36*(2), 228-239. https://doi.org/10.1016/j.psyneuen.2010.07.013

Cabral-Santos, C., Castrillón, C. I., Miranda, R. A., Monteiro, P. A., Inoue, D. S., Campos, E. Z., Hofmann, P., & Lira, F. S. (2016). Inflammatory cytokines and bdnf response to high-intensity intermittent exercise: Effect the exercise volume. *Frontiers in Physiology*, *7*, 509. https://doi.org/10.3389/fphys.2016.00509

Calignano, A., La Rana, G., Giuffrida, A., & Piomelli, D. (1998). Control of pain initiation by endogenous cannabinoids. *Nature*, *394*(6690), 277-281. https://doi.org/10.1038/28393

Campos, A. C., Brant, F., Miranda, A. S., Machado, F. S., & Teixeira, A. L. (2015). Cannabidiol increases survival and promotes rescue of cognitive function in a murine model of cerebral malaria. *Neuroscience*, *289*, 166-180. https://doi.org/10.1016/j.neuroscience.2014.12.051

Campos, A. C., Fogaça, M. V., Scarante, F. F., Joca, S. R. L., Sales, A. J., Gomes, F. V., Sonego, A. B., Rodrigues, N. S., Galve-Roperh, I., & Guimarães, F. S. (2017). Plastic and neuroprotective mechanisms involved in the therapeutic effects of cannabidiol in psychiatric disorders. *Frontiers in Pharmacology*, *8*, 269. https://doi.org/10.3389/fphar.2017.00269

Campos, A. C., Fogaça, M. V., Sonego, A. B., & Guimarães, F. S. (2016). Cannabidiol, neuroprotection and neuropsychiatric disorders. *Pharmacol Res*, *112*, 119-127. https://doi.org/10.1016/j.phrs.2016.01.033

Carlini, E. A., & Cunha, J. M. (1981). Hypnotic and antiepileptic effects of cannabidiol. *Journal of Clinical Pharmacology*, *21*(S1), 417S-427S. https://doi.org/10.1002/j.1552-4604.1981.tb02622.x

Castellano, V., & White, L. J. (2008). Serum brain-derived neurotrophic factor response to aerobic exercise in multiple sclerosis. *Journal of the Neurological Sciences, 269*(1-2), 85-91. https://doi.org/10.1016/j.jns.2007.12.030

Centers for Disease Control. (2022). *Physical activity guidelines and recommendations*. U.S. Department of Health & Human Services. https://www.cdc.gov/physicalactivity/resources/recommendations.html

Chen, M. H., Hsu, J. W., Huang, K. L., Tsai, S. J., Su, T. P., Li, C. T., Lin, W. C., Tu, P. C., & Bai, Y. M. (2021). Role of obesity in systemic low-grade inflammation and cognitive function in patients with bipolar i disorder or major depressive disorder. *CNS Spectrums, 26*(5), 521-527. https://doi.org/10.1017/S1092852920001534

Chen, X., Zhao, B., Qu, Y., Chen, Y., Xiong, J., Feng, Y., Men, D., Huang, Q., Liu, Y., Yang, B., Ding, J., & Li, F. (2020). Detectable serum severe acute respiratory syndrome coronavirus 2 viral load (rnaemia) is closely correlated with drastically elevated interleukin 6 level in critically ill patients with coronavirus disease 2019. *Clinical Infectious Diseases, 71*(8), 1937-1942. https://doi.org/10.1093/cid/ciaa449

Chiarlone, A., Bellocchio, L., Blázquez, C., Resel, E., Soria-Gómez, E., Cannich, A., Ferrero, J. J., Sagredo, O., Benito, C., Romero, J., Sánchez-Prieto, J., Lutz, B., Fernández-Ruiz, J., Galve-Roperh, I., & Guzmán, M. (2014). A restricted population of cb1 cannabinoid receptors with neuroprotective activity. *Proc Natl Acad Sci U S A, 111*(22), 8257-8262. https://doi.org/10.1073/pnas.1400988111

Cipryan, L., Svagera, Z., & Vala, R. (2015). Il-6 and crp response to maximal exercise intervention. *Journal of Sports Medicine and Physical Fitness, 55*(7-8), 813-823. https://pubmed.ncbi.nlm.nih.gov/25678206/

Cochrane-Snyman, K. C., Cruz, C., Morales, J., & Coles, M. (2021). The effects of cannabidiol oil on noninvasive measures of muscle damage in men. *Medicine and Science in Sports and Exercise, 53*(7), 1460-1472. https://doi.org/10.1249/mss.0000000000002606

Colbert, L. H., Visser, M., Simonsick, E. M., Tracy, R. P., Newman, A. B., Kritchevsky, S. B., Pahor, M., Taaffe, D. R., Brach, J., & Rubin, S. (2004). Physical activity, exercise, and inflammatory markers in older adults: Findings from the health, aging and body composition study. *J Am Geriatr Soc, 52*(7), 1098-1104. https://doi.org/10.1111/j.1532-5415.2004.52307.x

Collins, J. M., Hill, E., Bindoff, A., King, A. E., Alty, J., Summers, M. J., & Vickers, J. C. (2021). Association between components of cognitive reserve and serum bdnf in healthy older adults. *Frontiers in Aging Neuroscience, 13*, 725914. https://doi.org/10.3389/fnagi.2021.725914

Consroe, P., Sandyk, R., & Snider, S. R. (1986). Open label evaluation of cannabidiol in dystonic movement disorders. *International Journal of Neuroscience, 30*(4), 277-282. https://doi.org/10.3109/00207458608985678

Cooper, Z. D., & Craft, R. M. (2018). Sex-dependent effects of cannabis and cannabinoids: A translational perspective. *Neuropsychopharmacology, 43*(1), 34-51. https://doi.org/10.1038/npp.2017.140

Corroon, J., & Phillips, J. A. (2018). A cross-sectional study of cannabidiol users. *Cannabis Cannabinoid Research, 3*(1), 152-161. https://doi.org/10.1089/can.2018.0006

Couch, D. G., Tasker, C., Theophilidou, E., Lund, J. N., & O'Sullivan, S. E. (2017). Cannabidiol and palmitoylethanolamide are anti-inflammatory in the acutely inflamed human colon. *Clinical Science, 131*(21), 2611-2626. https://doi.org/10.1042/cs20171288

Crane, N. A., Schuster, R. M., Fusar-Poli, P., & Gonzalez, R. (2013). Effects of cannabis on neurocognitive functioning: Recent advances, neurodevelopmental influences, and sex differences. *Neuropsychology Review*, *23*(2), 117-137. https://doi.org/10.1007/s11065-012-9222-1

Crane, N. A., Schuster, R. M., & Gonzalez, R. (2013). Preliminary evidence for a sex-specific relationship between amount of cannabis use and neurocognitive performance in young adult cannabis users. *Journal of the International Neuropsychological Society*, *19*(9), 1009-1015. https://doi.org/10.1017/s135561771300088x

Crane, N. A., Schuster, R. M., Mermelstein, R. J., & Gonzalez, R. (2015). Neuropsychological sex differences associated with age of initiated use among young adult cannabis users. *Journal of Clinical and Experimental Neuropsychology*, *37*(4), 389-401. https://doi.org/10.1080/13803395.2015.1020770

Crippa, J. A., Zuardi, A. W., Garrido, G. E., Wichert-Ana, L., Guarnieri, R., Ferrari, L., Azevedo-Marques, P. M., Hallak, J. E., McGuire, P. K., & Filho Busatto, G. (2004). Effects of cannabidiol (cbd) on regional cerebral blood flow. *Neuropsychopharmacology*, *29*(2), 417-426. https://doi.org/10.1038/sj.npp.1300340

Cuñetti, L., Manzo, L., Peyraube, R., Arnaiz, J., Curi, L., & Orihuela, S. (2018). Chronic pain treatment with cannabidiol in kidney transplant patients in uruguay. *Transplantation* Proceedings, 50(2), 461-464. https://doi.org/10.1016/j.transproceed.2017.12.042

Dagmar, S., Erik, S., Karel, F., & Aleš, S. (2011). Gender differences in physical activity, sedentary behavior and bmi in the liberec region: The ipaq study in 2002-2009. *Journal of Human Kinetics*, *28*, 123-131. https://doi.org/10.2478/v10078-011-0029-6

De la Rosa, A., Solana, E., Corpas, R., Bartrés-Faz, D., Pallàs, M., Vina, J., Sanfeliu, C., & Gomez-Cabrera, M. C. (2019). Long-term exercise training improves memory in middle-aged men and modulates peripheral levels of bdnf and cathepsin b. *Scientific Reports*, *9*(1), 3337. https://doi.org/10.1038/s41598-019-40040-8

Dempster, P., & Aitkens, S. (1995). A new air displacement method for the determination of human body composition. *Medicine and Science in Sports and Exercise*, *27*(12), 1692-1697. https://pubmed.ncbi.nlm.nih.gov/8614327/

Devinsky, O., Cilio, M. R., Cross, H., Fernandez-Ruiz, J., French, J., Hill, C., Katz, R., Di Marzo, V., Jutras-Aswad, D., & Notcutt, W. G. (2014). Cannabidiol: Pharmacology and potential therapeutic role in epilepsy and other neuropsychiatric disorders. *Epilepsia*, *55*(6), 791-802. https://doi.org/10.1111/epi.12631

Devinsky, O., Cross, J. H., Laux, L., Marsh, E., Miller, I., Nabbout, R., Scheffer, I. E., Thiele, E. A., & Wright, S. (2017). Trial of cannabidiol for drug-resistant seizures in the dravet syndrome. *New England Journal of Medicine*, *376*(21), 2011-2020. https://doi.org/10.1056/NEJMoa1611618

Devinsky, O., Patel, A. D., Cross, J. H., Villanueva, V., Wirrell, E. C., Privitera, M., Greenwood, S. M., Roberts, C., Checketts, D., & VanLandingham, K. E. (2018). Effect of cannabidiol on drop seizures in the lennox–gastaut syndrome. *New England Journal of Medicine*, *378*(20), 1888-1897. https://doi.org/10.1056/NEJMoa1714631

Dieli-Conwright, C. M., Parmentier, J. H., Sami, N., Lee, K., Spicer, D., Mack, W. J., Sattler, F., & Mittelman, S. D. (2018). Adipose tissue inflammation in breast cancer survivors: Effects of a 16-week combined aerobic and resistance exercise training intervention. *Breast Cancer Research and Treatment*, *168*(1), 147-157. https://doi.org/10.1007/s10549-017-4576-y

Di Fabio, A., & Palazzeschi, L. (2015). Hedonic and eudaimonic well-being: The role of resilience beyond fluid intelligence and personality traits. *Frontiers in Psychology*, *6*, 1367. https://doi.org/10.3389/fpsyg.2015.01367

Di Marzo, V. (2018). New approaches and challenges to targeting the endocannabinoid system. *Nature Reviews Drug Discovery*, *17*(9), 623-639. https://doi.org/10.1038/nrd.2018.115

Di Marzo, V., & De Petrocellis, L. (2012). Why do cannabinoid receptors have more than one endogenous ligand? *Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences*, *367*(1607), 3216-3228. https://doi.org/10.1098/rstb.2011.0382

Ding, H., Chen, J., Su, M., Lin, Z., Zhan, H., Yang, F., Li, W., Xie, J., Huang, Y., Liu, X., Liu, B., & Zhou, X. (2020). Bdnf promotes activation of astrocytes and microglia contributing to neuroinflammation and mechanical allodynia in cyclophosphamide-induced cystitis. *Journal of Neuroinflammation*, *17*(1), 19. https://doi.org/10.1186/s12974-020-1704-0

Dong, R., Zhao, N. O., Wu, H. E., Yu, L., & Zhang, X. Y. (2021). Sex differences in the association between serum bdnf and cognitive impairment in schizophrenia patients using various antipsychotics. *Journal of Psychiatric Research*, *138*, 492-499. https://doi.org/10.1016/j.jpsychires.2021.04.026

Dow-Edwards, D. (2020). Sex differences in the interactive effects of early life stress and the endocannabinoid system. *Neurotoxicology and Teratology, 80*, 106893. https://doi.org/10.1016/j.ntt.2020.106893

Durst, R., Danenberg, H., Gallily, R., Mechoulam, R., Meir, K., Grad, E., Beeri, R., Pugatsch, T., Tarsish, E., & Lotan, C. (2007). Cannabidiol, a nonpsychoactive cannabis constituent, protects against myocardial ischemic reperfusion injury. *American Journal of Physiology-Heart and Circulatory Physiology*, *293*(6), H3602-3607. https://doi.org/10.1152/ajpheart.00098.2007

Dyrstad, S. M., Hansen, B. H., Holme, I. M., & Anderssen, S. A. (2014). Comparison of self-reported versus accelerometer-measured physical activity. *Medicine and Science in Sports and Exercise*, *46*(1), 99-106. https://doi.org/10.1249/MSS.0b013e3182a0595f

Edwards, K. M., Burns, V. E., Ring, C., & Carroll, D. (2006). Sex differences in the interleukin-6 response to acute psychological stress. *Biological Psychology*, *71*(3), 236-239. https://doi.org/10.1016/j.biopsycho.2005.06.006

Eggers, S., Ohnesorg, T., & Sinclair, A. (2014). Genetic regulation of mammalian gonad development. *Nature Reviews Endocrinology*, *10*(11), 673. https://doi.org/10.1038/nrendo.2014.163

Elms, L., Shannon, S., Hughes, S., & Lewis, N. (2019). Cannabidiol in the treatment of post-traumatic stress disorder: A case series. *Journal of Integrative and Complementary Medicine*, *25*(4), 392-397. https://doi.org/10.1089/acm.2018.0437

Elsner, V. R., Dorneles, G. P., Santos, M. A., da Silva, I. M., Romão, P., & Peres, A. (2020). Exercise-induced bdnf production by mononuclear cells of sedentary and physically active obese men. *Journal of Sports Medicine and Physical Fitness*, *60*(3), 435-441. https://doi.org/10.23736/s0022-4707.19.10113-2

Enns, D. L., & Tiidus, P. M. (2008). Estrogen influences satellite cell activation and proliferation following downhill running in rats. *Journal of Applied Physiology*, *104*(2), 347-353. https://doi.org/10.1152/japplphysiol.00128.2007

Enns, D. L., & Tiidus, P. M. (2010). The influence of estrogen on skeletal muscle. *Sports Medicine*, *40*(1), 41-58. https://doi.org/10.2165/11319760-000000000-00000

Erickson, K. I., Voss, M. W., Prakash, R. S., Basak, C., Szabo, A., Chaddock, L., Kim, J. S., Heo, S., Alves, H., White, S. M., Wojcicki, T. R., Mailey, E., Vieira, V. J., Martin, S. A., Pence, B. D., Woods, J. A., McAuley, E., & Kramer, A. F. (2011). Exercise training increases size of hippocampus and improves memory. *Proc Natl Acad Sci U S A*, *108*(7), 3017-3022. https://doi.org/10.1073/pnas.1015950108

Esposito, G., Scuderi, C., Valenza, M., Togna, G. I., Latina, V., De Filippis, D., Cipriano, M., Carratù, M. R., Iuvone, T., & Steardo, L. (2011). Cannabidiol reduces aβ-induced neuroinflammation and promotes hippocampal neurogenesis through pparγ involvement. *PLoS One*, *6*(12), e28668. https://doi.org/10.1371/journal.pone.0028668

Evert, D. L., & Oscar-Berman, M. (1995). Alcohol-related cognitive impairments: An overview of how alcoholism may affect the workings of the brain. *Alcohol Health and Research World*, *19*(2), 89-96. https://pubmed.ncbi.nlm.nih.gov/31798082/

Fanaei, H., Karimian, S. M., Sadeghipour, H. R., Hassanzade, G., Kasaeian, A., Attari, F., Khayat, S., Ramezani, V., & Javadimehr, M. (2014). Testosterone enhances functional recovery after stroke through promotion of antioxidant defenses, bdnf levels and neurogenesis in male rats. *Brain Research 1558*, 74-83. https://doi.org/10.1016/j.brainres.2014.02.028

Farrimond, J. A., Whalley, B. J., & Williams, C. M. (2012). Cannabinol and cannabidiol exert opposing effects on rat feeding patterns. *Psychopharmacology (Berl)*, *223*(1), 117-129. https://doi.org/10.1007/s00213-012-2697-x

Fattore, L., & Fratta, W. (2010). How important are sex differences in cannabinoid action? *Br J Pharmacol*, *160*(3), 544-548. https://doi.org/10.1111/j.1476-5381.2010.00776.x

Fedorova, E. V., Wong, C. F., Ataiants, J., Iverson, E., Conn, B. M., & Lankenau, S. E. (2021). Cannabidiol (cbd) and other drug use among young adults who use cannabis in los angeles. *Drug and Alcohol Dependence*, *221*, 108648. https://doi.org/10.1016/j.drugalcdep.2021.108648

Fernandez-Real, J.-M., Vayreda, M., Richart, C., Gutierrez, C., Broch, M., Vendrell, J., & Ricart, W. (2001). Circulating interleukin 6 levels, blood pressure, and insulin sensitivity in apparently healthy men and women. *Journal of Clinical Endocrinology and Metabolism*, *86*(3), 1154-1159. https://doi.org/10.1210/jcem.86.3.7305

Festa, A., D'Agostino, R., Jr., Williams, K., Karter, A., Mayer-Davis, E., Tracy, R., & Haffner, S. (2001). The relation of body fat mass and distribution to markers of chronic inflammation. *International Journal of Obesity and Related Metabolic Disorders*, *25*(10), 1407-1415. https://doi.org/10.1038/sj.ijo.0801792

Fine, P. G., & Rosenfeld, M. J. (2013). The endocannabinoid system, cannabinoids, and pain. *Rambam Maimonides Medical Journal, 4*(4), e0022. https://doi.org/10.5041/RMMJ.10129

Fioranelli, M., Bottaccioli, A. G., Bottaccioli, F., Bianchi, M., Rovesti, M., & Roccia, M. G. (2018). Stress and inflammation in coronary artery disease: A review psychoneuroendocrineimmunology-based. *Frontiers in Immunology, 9,* 2031. https://doi.org/10.3389/fimmu.2018.02031

Fischer, C. P. (2006). Interleukin-6 in acute exercise and training: What is the biological relevance? *Exercise Immunology Review, 12,* 6-33. http://www.ncbi.nlm.nih.gov/pubmed/17201070

Food and Drug Administration. (2020, November 19). *Scientific conference: Cbd and other cannabinoids: Sex and gender differences in use and responses* [virtual meeting]. Office of Women's Health Research. https://www.fda.gov/science-research/womens-health-research/scientific-conference-cbd-and-other-cannabinoids-sex-and-gender-differences-use-and-responses

Forti, L. N., Van Roie, E., Njemini, R., Coudyzer, W., Beyer, I., Delecluse, C., & Bautmans, I. (2017). Effects of resistance training at different loads on inflammatory markers in young adults. *European Journal of Applied Physiology, 117*(3), 511-519. https://doi.org/10.1007/s00421-017-3548-6

Fortress, A. M., Kim, J., Poole, R. L., Gould, T. J., & Frick, K. M. (2014). 17β-estradiol regulates histone alterations associated with memory consolidation and increases bdnd promoter acetylation in middle-aged female mice. *Learning & Memory, 21*(9), 457-467. https://doi.org/10.1101/lm.034033.113

Frazzitta, G., Maestri, R., Ghilardi, M. F., Riboldazzi, G., Perini, M., Bertotti, G., Boveri, N., Buttini, S., Lombino, F. L., Uccellini, D., Turla, M., Pezzoli, G., & Comi, C. (2014). Intensive rehabilitation increases bdnf serum levels in parkinsonian patients: A randomized study. *Neurorehabilitation & Neural Repair*, *28*(2), 163-168. https://doi.org/10.1177/1545968313508474

Fujimura, H., Altar, C. A., Chen, R., Nakamura, T., Nakahashi, T., Kambayashi, J., Sun, B., & Tandon, N. N. (2002). Brain-derived neurotrophic factor is stored in human platelets and released by agonist stimulation. *Journal of Thrombosis and Haemostasis*, *87*(4), 728-734.

Fumagalli, F., Racagni, G., & Riva, M. (2006). The expanding role of bdnf: A therapeutic target for alzheimer's disease? *Pharmacogenomics Journal*, *6*(1), 8-15. https://doi.org/10.1038/sj.tpj.6500337

Gabay, C., & Kushner, I. (1999). Acute-phase proteins and other systemic responses to inflammation. *New England Journal of Medicine, 340*(6), 448-454. https://doi.org/10.1056/NEJM199902113400607

Gáll, Z., Farkas, S., Albert, Á., Ferencz, E., Vancea, S., Urkon, M., & Kolcsár, M. (2020). Effects of chronic cannabidiol treatment in the rat chronic unpredictable mild stress model of depression. *Biomolecules*, *10*(5), 801. https://doi.org/10.3390/biom10050801

Gaoni, Y., & Mechoulam, R. (1964). Isolation, structure, and partial synthesis of an active constituent of hashish. *Journal of the American Chemical Society*, *86*(8), 1646-1647.

Gillman, A. S., Hutchison, K. E., & Bryan, A. D. (2015). Cannabis and exercise science: A commentary on existing studies and suggestions for future directions. *Sports Medicine, 45*(10), 1357-1363. https://doi.org/10.1007/s40279-015-0362-3

Glud, M., Christiansen, T., Larsen, L. H., Richelsen, B., & Bruun, J. M. (2019). Changes in circulating bdnf in relation to sex, diet, and exercise: A 12-week randomized controlled study in overweight and obese participants. *Journal of Obesity, 2019,* 4537274. https://doi.org/10.1155/2019/4537274

Gold, S. M., Schulz, K.-H., Hartmann, S., Mladek, M., Lang, U. E., Hellweg, R., Reer, R., Braumann, K.-M., & Heesen, C. (2003). Basal serum levels and reactivity of nerve growth factor and brain-derived neurotrophic factor to standardized acute exercise in multiple sclerosis and controls. *Journal of Neuroimmunology, 138*(1), 99-105. https://doi.org/10.1016/s0165-5728(03)00121-8

Goldstein, B. I., Collinger, K. A., Lotrich, F., Marsland, A. L., Gill, M. K., Axelson, D. A., & Birmaher, B. (2011). Preliminary findings regarding proinflammatory markers and brain-derived neurotrophic factor among adolescents with bipolar spectrum disorders. *Journal of Child and Adolescent Psychopharmacology, 21*(5), 479-484. https://doi.org/10.1089/cap.2011.0009

Gomarasca, M., Banfi, G., & Lombardi, G. (2020). Myokines: The endocrine coupling of skeletal muscle and bone. *Advances in Clinical Chemistry, 94*, 155-218. https://doi.org/10.1016/bs.acc.2019.07.010

Gomes, C., Ferreira, R., George, J., Sanches, R., Rodrigues, D. I., Gonçalves, N., & Cunha, R. A. (2013). Activation of microglial cells triggers a release of brain-derived neurotrophic factor (bdnf) inducing their proliferation in an adenosine a2a receptor-dependent manner: A2a receptor blockade prevents bdnf release and proliferation of microglia. *Journal of Neuroinflammation, 10*(1), 16. https://doi.org/10.1186/1742-2094-10-16

Gratacos, J., Collado, A., Filella, X., Sanmarti, R., Canete, J., Llena, J., Molina, R., Ballesta, A., & Muñoz-Gómez, J. (1994). Serum cytokines (il-6, tnf-α, il-1β and ifn-γ) in ankylosing spondylitis: A close correlation between serum il-6 and disease activity and severity. *British Journal of Rheumatology*, *33*(10), 927-931. https://doi.org/10.1093/rheumatology/33.10.927

Green, T., Flash, S., & Reiss, A. L. (2019). Sex differences in psychiatric disorders: What we can learn from sex chromosome aneuploidies. *Neuropsychopharmacology*, *44*(1), 9-21. https://doi.org/10.1038/s41386-018-0153-2

Greenwald, A. G., McGhee, D. E., & Schwartz, J. L. (1998). Measuring individual differences in implicit cognition: The implicit association test. *Journal of Personality and Social Psychology*, *74*(6), 1464. https://doi.org/10.1037//0022-3514.74.6.1464

Guo, L., Ren, L., & Zhang, C. (2018). Relationship between depression and inflammatory factors and brain-derived neurotrophic factor in patients with perimenopause syndrome. *Experimental and Therapeutic Medicine*, *15*(5), 4436-4440. https://doi.org/10.3892/etm.2018.5985

Hackett, R. A., Hamer, M., Endrighi, R., Brydon, L., & Steptoe, A. (2012). Loneliness and stress-related inflammatory and neuroendocrine responses in older men and women. *Psychoneuroendocrinology*, *37*(11), 1801-1809. https://doi.org/10.1016/j.psyneuen.2012.03.016

Hallak, J. E., Machado-de-Sousa, J. P., Crippa, J. A. S., Sanches, R. F., Trzesniak, C., Chaves, C., Bernardo, S. A., Regalo, S. C., & Zuardi, A. W. (2010). Performance of schizophrenic patients in the stroop color word test and electrodermal responsiveness after acute administration of cannabidiol (cbd). *Brazilian Journal of Psychiatry*, *32*(1), 56-61. https://doi.org/10.1590/s1516-44462010000100011

Han, Y. X., Tao, C., Gao, X. R., Wang, L. L., Jiang, F. H., Wang, C., Fang, K., Chen, X. X., Chen, Z., & Ge, J. F. (2018). Bdnf-related imbalance of copine 6 and synaptic plasticity markers couples with depression-like behavior and immune activation in cums rats. *Frontiers in Neuroscience*, *12*, 731. https://doi.org/10.3389/fnins.2018.00731

Haney, M., Malcolm, R. J., Babalonis, S., Nuzzo, P. A., Cooper, Z. D., Bedi, G., Gray, K. M., McRae-Clark, A., Lofwall, M. R., Sparenborg, S., & Walsh, S. L. (2016). Oral cannabidiol does not alter the subjective, reinforcing or cardiovascular effects of smoked cannabis. *Neuropsychopharmacology*, *41*(8), 1974-1982. https://doi.org/10.1038/npp.2015.367

Hardee, J. P., Fix, D. K., Wang, X., Goldsmith, E. C., Koh, H. J., & Carson, J. A. (2018). Systemic il-6 regulation of eccentric contraction-induced muscle protein synthesis. *American Journal of Physiology-Cell Physiology*, *315*(1), C91-c103. https://doi.org/10.1152/ajpcell.00063.2018

Haskell, W. L., Lee, I. M., Pate, R. R., Powell, K. E., Blair, S. N., Franklin, B. A., Macera, C. A., Heath, G. W., Thompson, P. D., & Bauman, A. (2007). Physical activity and public health: Updated recommendation for adults from the american college of sports medicine and the american heart association. *Medicine and Science in Sports and Exercise*, *39*(8), 1423-1434. https://doi.org/10.1249/mss.0b013e3180616b27

He, J. Y., Wei, X. H., Li, S. J., Liu, Y., Hu, H. L., Li, Z. Z., Kuang, X. H., Wang, L., Shi, X., Yuan, S. T., & Sun, L. (2018). Adipocyte-derived il-6 and leptin promote breast cancer metastasis via upregulation of lysyl hydroxylase-2 expression. *Cell Communication and Signaling*, *16*(1), 100. https://doi.org/10.1186/s12964-018-0309-z

Herder, C., Schneitler, S., Rathmann, W., Haastert, B., Schneitler, H., Winkler, H., Bredahl, R., Hahnloser, E., & Martin, S. (2007). Low-grade inflammation, obesity, and insulin resistance in adolescents. *Journal of Clinical Endocrinology & Metabolism*, *92*(12), 4569-4574. https://doi.org/10.1210/jc.2007-0955

Hofer, M., Pagliusi, S. R., Hohn, A., Leibrock, J., & Barde, Y. A. (1990). Regional distribution of brain-derived neurotrophic factor mrna in the adult mouse brain. *EMBO Journal*, *9*(8), 2459-2464. https://doi.org/10.1002/j.1460-2075.1990.tb07423.x

Huestis, M. A., Solimini, R., Pichini, S., Pacifici, R., Carlier, J., & Busardò, F. P. (2019). Cannabidiol adverse effects and toxicity. *Curr Neuropharmacol*, *17*(10), 974-989. https://doi.org/10.2174/1570159x17666190603171901

Hughto, J. M., Quinn, E. K., Dunbar, M. S., Rose, A. J., Shireman, T. I., & Jasuja, G. K. (2021). Prevalence and co-occurrence of alcohol, nicotine, and other substance use disorder diagnoses among us transgender and cisgender adults. *JAMA Network Open*, *4*(2), e2036512. https://doi.org/10.1001/jamanetworkopen.2020.36512

Hurel, I., Muguruza, C., Redon, B., Marsicano, G., & Chaouloff, F. (2021). Cannabis and exercise: Effects of delta(9)-tetrahydrocannabinol on preference and motivation for wheel-running in mice. *Prog Neuropsychopharmacol Biol Psychiatry*, *105*, 110117. https://doi.org/10.1016/j.pnpbp.2020.110117

Ihara, K., Yoshida, H., Jones, P. B., Hashizume, M., Suzuki, Y., Ishijima, H., Kim, H. K., Suzuki, T., & Hachisu, M. (2016). Serum bdnf levels before and after the development of mood disorders: A case–control study in a population cohort. *Translational Psychiatry 6*(4), e782-e782. https://doi.org/10.1038/tp.2016.47

Irving, P. M., Iqbal, T., Nwokolo, C., Subramanian, S., Bloom, S., Prasad, N., Hart, A., Murray, C., Lindsay, J. O., & Taylor, A. (2018). A randomized, double-blind, placebo-controlled, parallel-group, pilot study of cannabidiol-rich botanical extract in the symptomatic treatment of ulcerative colitis. *Inflammatory Bowel Disease*, *24*(4), 714-724. https://doi.org/10.1093/ibd/izy002

Isenmann, E., Veit, S., Starke, L., Flenker, U., & Diel, P. (2021). Effects of cannabidiol supplementation on skeletal muscle regeneration after intensive resistance training. *Nutrients*, *13*(9). https://doi.org/10.3390/nu13093028

Iverson, G. L., Marsh, J. M., Connors, E. J., & Terry, D. P. (2021). Normative reference values, reliability, and item-level symptom endorsement for the promis® v2.0 cognitive function-short forms 4a, 6a and 8a. *Archives of Clinical Neuropsychology*, *36*(7), 1341-1349. https://doi.org/10.1093/arclin/acaa128

Jadoon, K. A., Ratcliffe, S. H., Barrett, D. A., Thomas, E. L., Stott, C., Bell, J. D., O'Sullivan, S. E., & Tan, G. D. (2016). Efficacy and safety of cannabidiol and tetrahydrocannabivarin on glycemic and lipid parameters in patients with type 2 diabetes: A randomized, double-blind, placebo-controlled, parallel group pilot study. *Diabetes Care*, *39*(10), 1777-1786.

Javadi-Paydar, M., Nguyen, J. D., Kerr, T. M., Grant, Y., Vandewater, S. A., Cole, M., & Taffe, M. A. (2018). Effects of δ9-thc and cannabidiol vapor inhalation in male and female rats. *Psychopharmacology*, *235*(9), 2541-2557. https://doi.org/10.1007/s00213-018-4946-0

Jehn, C. F., Becker, B., Flath, B., Nogai, H., Vuong, L., Schmid, P., & Lüftner, D. (2015). Neurocognitive function, brain-derived neurotrophic factor (bdnf) and il-6 levels in cancer patients with depression. *Journal of Neuroimmunology, 287*, 88-92. https://doi.org/https://doi.org/10.1016/j.jneuroim.2015.08.012

Jimenez Naranjo, C., Osborne, A. L., & Weston-Green, K. (2019). Effect of cannabidiol on muscarinic neurotransmission in the pre-frontal cortex and hippocampus of the poly i:C rat model of schizophrenia. *Prog Neuropsychopharmacol Biol Psychiatry*, *94*, 109640. https://doi.org/https://doi.org/10.1016/j.pnpbp.2019.109640

Jovanović, V. (2015). Structural validity of the mental health continuum-short form: The bifactor model of emotional, social and psychological well-being. *Personality and Individual Differences*, *75*, 154-159. https://doi.org/10.1016/j.paid.2014.11.026

Kaczkurkin, A. N., Raznahan, A., & Satterthwaite, T. D. (2019). Sex differences in the developing brain: Insights from multimodal neuroimaging. *Neuropsychopharmacology*, *44*(1), 71-85. https://doi.org/10.1038/s41386-018-0111-z

Kallies, G., Rapp, M. A., Fydrich, T., Fehm, L., Tschorn, M., Terán, C., Schwefel, M., Pietrek, A., Henze, R., Hellweg, R., Ströhle, A., Heinzel, S., & Heissel, A. (2019). Serum brain-derived neurotrophic factor (bdnf) at rest and after acute aerobic exercise in major depressive disorder. *Psychoneuroendocrinology, 102*, 212-215. https://doi.org/10.1016/j.psyneuen.2018.12.015

Kang, H. J., Kim, J. M., Kim, S. Y., Kim, S. W., Shin, I. S., Kim, H. R., Park, M. H., Shin, M. G., Yoon, J. H., & Yoon, J. S. (2015). A longitudinal study of bdnf promoter methylation and depression in breast cancer. *Psychiatry Investigation*, *12*(4), 523-531. https://doi.org/10.4306/pi.2015.12.4.523

Karlović, D., Serretti, A., Vrkić, N., Martinac, M., & Marčinko, D. (2012). Serum concentrations of crp, il-6, tnf-α and cortisol in major depressive disorder with melancholic or atypical features. *Psychiatric Research, 198*(1), 74-80. https://doi.org/10.1016/j.psychres.2011.12.007

Karmaus, P. W., Wagner, J. G., Harkema, J. R., Kaminski, N. E., & Kaplan, B. L. (2013). Cannabidiol (cbd) enhances lipopolysaccharide (lps)-induced pulmonary inflammation in c57bl/6 mice. *Journal of Immunotoxicology, 10*(3), 321-328. https://doi.org/10.3109/1547691X.2012.741628

Karsenty, G., & Ferron, M. (2012). The contribution of bone to whole-organism physiology. *Nature, 481*(7381), 314-320. https://doi.org/10.1038/nature10763

Karsenty, G., & Mera, P. (2018). Molecular bases of the crosstalk between bone and muscle. *Bone, 115*, 43-49.

Kasapis, C., & Thompson, P. D. (2005). The effects of physical activity on serum c-reactive protein and inflammatory markers: A systematic review. *Journal of the American College of Cardiology, 45*(10), 1563-1569. https://doi.org/10.1016/j.jacc.2004.12.077

Kasper, A. M., Sparks, S. A., Hooks, M., Skeer, M., Webb, B., Nia, H., Morton, J. P., & Close, G. L. (2020). High prevalence of cannabidiol use within male professional rugby union and league players: A quest for pain relief and enhanced recovery. *International Journal of Sport Nutrition and Exercise Metabolism, 30*(5), 315-322. https://doi.org/10.1123/ijsnem.2020-0151

Kennedy, M. C. (2017). Cannabis: Exercise performance and sport. A systematic review. *Journal of Science and Medicine in Sport, 20*(9), 825-829. https://doi.org/10.1016/j.jsams.2017.03.012

Kerschensteiner, M., Gallmeier, E., Behrens, L., Leal, V. V., Misgeld, T., Klinkert, W. E., Kolbeck, R., Hoppe, E., Oropeza-Wekerle, R. L., Bartke, I., Stadelmann, C., Lassmann, H., Wekerle, H., & Hohlfeld, R. (1999). Activated human t cells, b cells, and monocytes produce brain-derived neurotrophic factor in vitro and in inflammatory brain lesions: A neuroprotective role of inflammation? *Journal of Experimental Medicine*, *189*(5), 865-870. https://doi.org/10.1084/jem.189.5.865

Khan, A. A., Shekh-Ahmad, T., Khalil, A., Walker, M. C., & Ali, A. B. (2018). Cannabidiol exerts antiepileptic effects by restoring hippocampal interneuron functions in a temporal lobe epilepsy model. *Br J Pharmacol*, *175*(11), 2097-2115. https://doi.org/10.1111/bph.14202

Khera, A., Vega, G. L., Das, S. R., Ayers, C., McGuire, D. K., Grundy, S. M., & de Lemos, J. A. (2009). Sex differences in the relationship between c-reactive protein and body fat. *The Journal of Clinical Endocrinology & Metabolism*, *94*(9), 3251-3258. https://doi.org/10.1210/jc.2008-2406

Khreiss, T., József, L., Hossain, S., Chan, J. S., Potempa, L. A., & Filep, J. G. (2002). Loss of pentameric symmetry of c-reactive protein is associated with delayed apoptosis of human neutrophils. *Journal of Biological Chemistry*, *277*(43), 40775-40781. https://doi.org/10.1074/jbc.M205378200

Kim, Y., Ryu, J., Ryu, M. S., Lim, S., Han, K. O., Lim, I. K., & Han, K. H. (2014). C-reactive protein induces g2/m phase cell cycle arrest and apoptosis in monocytes through the upregulation of b-cell translocation gene 2 expression. *FEBS Letters*, *588*(4), 625-631. https://doi.org/10.1016/j.febslet.2014.01.008

Komulainen, J., Koskinen, S., Kalliokoski, R., Takala, T., & Vihko, V. (1999). Gender differences in skeletal muscle fibre damage after eccentrically biased downhill running in rats. *Acta Psychiatrica Scandinavica 165*(1), 57-63. https://doi.org/10.1046/j.1365-201x.1999.00481.x

Krebs-Kraft, D. L., Hill, M. N., Hillard, C. J., & McCarthy, M. M. (2010). Sex difference in cell proliferation in developing rat amygdala mediated by endocannabinoids has implications for social behavior. *Proceedings of the National Academy of Sciences*, *107*(47), 20535-20540. https://doi.org/10.1073/pnas.1005003107

Kumari, N., Dwarakanath, B. S., Das, A., & Bhatt, A. N. (2016). Role of interleukin-6 in cancer progression and therapeutic resistance. *Tumour Biol*, *37*(9), 11553-11572. https://doi.org/10.1007/s13277-016-5098-7

Laczkovics, C., Kothgassner, O. D., Felnhofer, A., & Klier, C. M. (2020). Cannabidiol treatment in an adolescent with multiple substance abuse, social anxiety and depression. *Neuropsychiatrie : Klinik, Diagnostik, Therapie und Rehabilitation : Organ der Gesellschaft Osterreichischer Nervenarzte und Psychiater*, *35*(1), 31-34. https://doi.org/10.1007/s40211-020-00334-0

Landers, M. R., Navalta, J. W., Murtishaw, A. S., Kinney, J. W., & Pirio Richardson, S. (2019). A high-intensity exercise boot camp for persons with parkinson disease: A phase ii, pragmatic, randomized clinical trial of feasibility, safety, signal of efficacy, and disease mechanisms. *Journal of Neurologic Physical Therapy*, *43*(1), 12-25. https://doi.org/10.1097/npt.0000000000000249

Lang, U. E., Hellweg, R., & Gallinat, J. (2004). Bdnf serum concentrations in healthy volunteers are associated with depression-related personality traits. *Neuropsychopharmacology*, *29*(4), 795-798.

Langer, H. T., Mossakowski, A. A., Pathak, S., Mascal, M., & Baar, K. (2021). Cannabidiol does not impair anabolic signaling following eccentric contractions in rats. *International Journal of Sport Nutrition and Exercise Metabolism*, *31*(2), 98-100. https://doi.org/10.1123/ijsnem.2020-0270

Laprairie, R. B., Bagher, A. M., Kelly, M. E., & Denovan-Wright, E. M. (2015). Cannabidiol is a negative allosteric modulator of the cannabinoid cb1 receptor. *Br J Pharmacol*, *172*(20), 4790-4805. https://doi.org/10.1111/bph.13250

Lear, S. A., Chen, M. M., Birmingham, C. L., & Frohlich, J. J. (2003). The relationship between simple anthropometric indices and c-reactive protein: Ethnic and gender differences. *Metabolism*, *52*(12), 1542-1546. https://doi.org/https://doi.org/10.1016/j.metabol.2003.07.005

Lee, Y., McKechnie, T., Doumouras, A. G., Handler, C., Eskicioglu, C., Gmora, S., Anvari, M., & Hong, D. (2019). Diagnostic value of c-reactive protein levels in postoperative infectious complications after bariatric surgery: A systematic review and meta-analysis. *Obesity Surgery*, *29*(7), 2022-2029. https://doi.org/10.1007/s11695-019-03832-5

Lentini, E., Kasahara, M., Arver, S., & Savic, I. (2013). Sex differences in the human brain and the impact of sex chromosomes and sex hormones. *Cerebral Cortex*, *23*(10), 2322-2336. https://doi.org/10.1093/cercor/bhs222

Lenz, K. M., & McCarthy, M. M. (2015). A starring role for microglia in brain sex differences. *Neuroscientist*, *21*(3), 306-321. https://doi.org/10.1177/1073858414536468

Lenz, K. M., & Nelson, L. H. (2018). Microglia and beyond: Innate immune cells as regulators of brain development and behavioral function. *Frontiers in Immunology*, *9*, 698. https://doi.org/10.3389/fimmu.2018.00698

Le Strat, Y., & Le Foll, B. (2011). Obesity and cannabis use: Results from 2 representative national surveys. *American journal of epidemiology*, *174*(8), 929-933. https://doi.org/10.1093/aje/kwr200

Leweke, F., Piomelli, D., Pahlisch, F., Muhl, D., Gerth, C., Hoyer, C., Klosterkötter, J., Hellmich, M., & Koethe, D. (2012). Cannabidiol enhances anandamide signaling and alleviates psychotic symptoms of schizophrenia. *Translational Psychiatry*, *2*(3), e94-e94. https://doi.org/10.1038/tp.2012.15

Li, G., Shang, Z., Liu, Y., Yan, H., & Ou, T. (2020). The diagnostic values of pretreatment serum inflammation markers and lipoprotein in men with total prostate-specific antigen between 4 and 10 ng/ml. *Frontiers in Medicine*, *7*, 576812. https://doi.org/10.3389/fmed.2020.576812

Libardi, C. A., De Souza, G. V., Cavaglieri, C. R., Madruga, V. A., & Chacon-Mikahil, M. P. T. (2012). Effect of resistance, endurance, and concurrent training on tnf-α, il-6, and crp. *Medicine and Science in Sports and Exercise*, *44*(1), 50-56. https://doi.org/10.1249/MSS.0b013e318229d2e9

Ligresti, A., De Petrocellis, L., & Di Marzo, V. (2016). From phytocannabinoids to cannabinoid receptors and endocannabinoids: Pleiotropic physiological and pathological roles through complex pharmacology. *Physiological Reviews*, *96*(4), 1593-1659. https://doi.org/10.1152/physrev.00002.2016

Linher-Melville, K., Zhu, Y. F., Sidhu, J., Parzei, N., Shahid, A., Seesankar, G., Ma, D., Wang, Z., Zacal, N., Sharma, M., Parihar, V., Zacharias, R., & Singh, G. (2020). Evaluation of the preclinical analgesic efficacy of naturally derived, orally administered oil forms of δ9-tetrahydrocannabinol (thc), cannabidiol (cbd), and their 1:1 combination. *PLoS One*, *15*(6), e0234176-e0234176. https://doi.org/10.1371/journal.pone.0234176

Lisano, J. K., Kisiolek, J. N., Smoak, P., Phillips, K. T., & Stewart, L. K. (2020). Chronic cannabis use and circulating biomarkers of neural health, stress, and inflammation in physically active individuals. *Applied Physiology, Nutrition, and Metabolism*, *45*(3), 258-263. https://doi.org/10.1139/apnm-2019-0300

Lisano, J. K., Phillips, K. T., Smith, J. D., Barnes, M. J., & Stewart, L. K. (2018). Patterns and perceptions of cannabis use with physical activity. *bioRxiv*, 328732. https://doi.org/10.1101/328732

Lisano, J. K., Smith, J. D., Mathias, A. B., Christensen, M., Smoak, P., Phillips, K. T., Quinn, C. J., & Stewart, L. K. (2019). Performance and health-related characteristics of physically active males using marijuana. *Journal of Strength & Conditioning Research*, *33*(6), 1658-1668. https://doi.org/10.1519/jsc.0000000000002238

Littlefield, A. M., Setti, S. E., Priester, C., & Kohman, R. A. (2015). Voluntary exercise attenuates lps-induced reductions in neurogenesis and increases microglia expression of a proneurogenic phenotype in aged mice. *Journal of Neuroinflammation*, *12*, 138. https://doi.org/10.1186/s12974-015-0362-0

Liu, C. H., Abrams, N. D., Carrick, D. M., Chander, P., Dwyer, J., Hamlet, M. R. J., Macchiarini, F., PrabhuDas, M., Shen, G. L., Tandon, P., & Vedamony, M. M. (2017). Biomarkers of chronic inflammation in disease development and prevention: Challenges and opportunities. *Nat Immunol*, *18*(11), 1175-1180. https://doi.org/10.1038/ni.3828

Liu, L. L., Li, J. M., Su, W. J., Wang, B., & Jiang, C. L. (2019). Sex differences in depressive-like behaviour may relate to imbalance of microglia activation in the hippocampus. *Brain Behav Immun*, *81*, 188-197. https://doi.org/10.1016/j.bbi.2019.06.012

Liu, Q. R., Pan, C. H., Hishimoto, A., Li, C. Y., Xi, Z. X., Llorente-Berzal, A., Viveros, M. P., Ishiguro, H., Arinami, T., Onaivi, E. S., & Uhl, G. R. (2009). Species differences in cannabinoid receptor 2 (cnr2 gene): Identification of novel human and rodent cb2 isoforms, differential tissue expression and regulation by cannabinoid receptor ligands. *Genes, Brain and Behavior*, *8*(5), 519-530. https://doi.org/10.1111/j.1601-183X.2009.00498.x

Lobo-Silva, D., Carriche, G. M., Castro, A. G., Roque, S., & Saraiva, M. (2016). Balancing the immune response in the brain: Il-10 and its regulation. *Journal of Neuroinflammation*, *13*(1), 297. https://doi.org/10.1186/s12974-016-0763-8

Lockwood, K. G., Marsland, A. L., Cohen, S., & Gianaros, P. J. (2016). Sex differences in the association between stressor-evoked interleukin-6 reactivity and c-reactive protein. *Brain Behav Immun*, *58*, 173-180. https://doi.org/10.1016/j.bbi.2016.07.001

Lopez, H. L., Cesareo, K. R., Raub, B., Kedia, A. W., Sandrock, J. E., Kerksick, C. M., & Ziegenfuss, T. N. (2020). Effects of hemp extract on markers of wellness, stress resilience, recovery and clinical biomarkers of safety in overweight, but otherwise healthy subjects. *J Diet Suppl*, *17*(5), 561-586. https://doi.org/10.1080/19390211.2020.1765941

Lovejoy, J., Sainsbury, A., & Group, S. C. W. (2009). Sex differences in obesity and the regulation of energy homeostasis. *Obesity Reviews*, *10*(2), 154-167. https://doi.org/10.1111/j.1467-789X.2008.00529.x

Luchicchi, A., & Pistis, M. (2012). Anandamide and 2-arachidonoylglycerol: Pharmacological properties, functional features, and emerging specificities of the two major endocannabinoids. *Mol Neurobiol*, *46*(2), 374-392. https://doi.org/10.1007/s12035-012-8299-0

Ludban, M., & Gitimu, P. (2015). *Psychological well-being of college students*. https://www.kon.org/urc/v14/ludban.html

Maachi, M., Pieroni, L., Bruckert, E., Jardel, C., Fellahi, S., Hainque, B., Capeau, J., & Bastard, J. (2004). Systemic low-grade inflammation is related to both circulating and adipose tissue tnf α, leptin and il-6 levels in obese women. *International Journal of Obesity and Related Metabolic Disorders*, *28*(8), 993-997. https://doi.org/10.1038/sj.ijo.0802718

MacNeil, L. G., Baker, S. K., Stevic, I., & Tarnopolsky, M. A. (2011). 17β-estradiol attenuates exercise-induced neutrophil infiltration in men. *American Journal of Physiology-Regulatory, Integrative and Comparative Physiology*, *300*(6), R1443-1451. https://doi.org/10.1152/ajpregu.00689.2009

Marconi, A., Di Forti, M., Lewis, C. M., Murray, R. M., & Vassos, E. (2016). Meta-analysis of the association between the level of cannabis use and risk of psychosis. *Schizophrenia Bulletin 42*(5), 1262-1269. https://doi.org/10.1093/schbul/sbw003

Maroon, J., & Bost, J. (2018). Review of the neurological benefits of phytocannabinoids. *Surg Neurol Int*, *9*, 91. https://doi.org/10.4103/sni.sni_45_18

Martin-Santos, R., a Crippa, J., Batalla, A., Bhattacharyya, S., Atakan, Z., Borgwardt, S., Allen, P., Seal, M., Langohr, K., & Farre, M. (2012). Acute effects of a single, oral dose of d9-tetrahydrocannabinol (thc) and cannabidiol (cbd) administration in healthy volunteers. *Current pharmaceutical design*, *18*(32), 4966-4979. https://doi.org/10.2174/138161212802884780

Marzolini, C., Stader, F., Stoeckle, M., Franzeck, F., Egli, A., Bassetti, S., Hollinger, A., Osthoff, M., Weisser, M., Gebhard, C. E., Baettig, V., Geenen, J., Khanna, N., Tschudin-Sutter, S., Mueller, D., Hirsch, H. H., Battegay, M., & Sendi, P. (2020). Effect of systemic inflammatory response to sars-cov-2 on lopinavir and hydroxychloroquine plasma concentrations. *Antimicrobial Agents and Chemotherapy*, *64*(9). https://doi.org/10.1128/aac.01177-20

Matheson, J., Sproule, B., Di Ciano, P., Fares, A., Le Foll, B., Mann, R. E., & Brands, B. (2020). Sex differences in the acute effects of smoked cannabis: Evidence from a human laboratory study of young adults. *Psychopharmacology (Berl)*, *237*(2), 305-316. https://doi.org/10.1007/s00213-019-05369-y

Matsuda, L. A., Lolait, S. J., Brownstein, M. J., Young, A. C., & Bonner, T. I. (1990). Structure of a cannabinoid receptor and functional expression of the cloned cdna. *Nature*, *346*(6284), 561-564. https://doi.org/10.1038/346561a0

Matthews, V. B., Aström, M. B., Chan, M. H., Bruce, C. R., Krabbe, K. S., Prelovsek, O., Akerström, T., Yfanti, C., Broholm, C., Mortensen, O. H., Penkowa, M., Hojman, P., Zankari, A., Watt, M. J., Bruunsgaard, H., Pedersen, B. K., & Febbraio, M. A. (2009). Brain-derived neurotrophic factor is produced by skeletal muscle cells in response to contraction and enhances fat oxidation via activation of amp-activated protein kinase. *Diabetologia*, *52*(7), 1409-1418. https://doi.org/10.1007/s00125-009-1364-1

Mattusch, F., Dufaux, B., Heine, O., Mertens, I., & Rost, R. (2000). Reduction of the plasma concentration of c-reactive protein following nine months of endurance training. *International Journal of Sports Medicine 21*(1), 21-24. https://doi.org/10.1055/s-2000-8852

Maud, P. J., & Shultz, B. B. (1986). Gender comparisons in anaerobic power and anaerobic capacity tests. *British Journal of Sports Medicine*, *20*(2), 51-54. https://doi.org/10.1136/bjsm.20.2.51

McCartney, D., Benson, M. J., Desbrow, B., Irwin, C., Suraev, A., & McGregor, I. S. (2020). Cannabidiol and sports performance: A narrative review of relevant evidence and recommendations for future research. *Sports Medicine - Open*, *6*(1), 1-18. https://doi.org/10.1186/s40798-020-00251-0

McDowell, I., Kristjansson, B., Hill, G., & Hebert, R. (1997). Community screening for dementia: The mini mental state exam (mmse) and modified mini-mental state exam (3ms) compared. *Journal of Clinical Epidemiology*, *50*(4), 377-383.

McEwen, B. S., & Milner, T. A. (2017). Understanding the broad influence of sex hormones and sex differences in the brain. *Journal of Neuroscience Research*, *95*(1-2), 24-39. https://doi.org/10.1002/jnr.23809

McGuire, P., Robson, P., Cubala, W. J., Vasile, D., Morrison, P. D., Barron, R., Taylor, A., & Wright, S. (2018). Cannabidiol (cbd) as an adjunctive therapy in schizophrenia: A multicenter randomized controlled trial. *American Journal of Psychiatry*, *175*(3), 225-231. https://doi.org/10.1176/appi.ajp.2017.17030325

McLean, C. P., Asnaani, A., Litz, B. T., & Hofmann, S. G. (2011). Gender differences in anxiety disorders: Prevalence, course of illness, comorbidity and burden of illness. *Journal of Psychiatric Research*, *45*(8), 1027-1035. https://doi.org/10.1016/j.jpsychires.2011.03.006

Medzhitov, R. (2008). Origin and physiological roles of inflammation. *Nature*, *454*(7203), 428-435. https://doi.org/10.1038/nature07201

Mendham, A. E., Donges, C. E., Liberts, E. A., & Duffield, R. (2011). Effects of mode and intensity on the acute exercise-induced il-6 and crp responses in a sedentary, overweight population. *European Journal of Applied Physiology*, *111*(6), 1035-1045. https://doi.org/10.1007/s00421-010-1724-z

Mogil, J. S. (2012). Sex differences in pain and pain inhibition: Multiple explanations of a controversial phenomenon. *Nature Reviews Neuroscience*, *13*(12), 859-866. https://doi.org/10.1038/nrn3360

Moltke, J., & Hindocha, C. (2021). Reasons for cannabidiol use: A cross-sectional study of cbd users, focusing on self-perceived stress, anxiety, and sleep problems. *Journal of Cannabis Research*, *3*(1), 5. https://doi.org/10.1186/s42238-021-00061-5

Moore, T. H., Zammit, S., Lingford-Hughes, A., Barnes, T. R., Jones, P. B., Burke, M., & Lewis, G. (2007). Cannabis use and risk of psychotic or affective mental health outcomes: A systematic review. *Lancet*, *370*(9584), 319-328. https://doi.org/10.1016/s0140-6736(07)61162-3

Moreno, C., Wykes, T., Galderisi, S., Nordentoft, M., Crossley, N., Jones, N., Cannon, M., Correll, C. U., Byrne, L., & Carr, S. (2020). How mental health care should change as a consequence of the covid-19 pandemic. *Lancet Psychiatry*, *7*(9), 813-824. https://doi.org/10.1016/S2215-0366(20)30307-2

Mori, M. A., Meyer, E., Soares, L. M., Milani, H., Guimarães, F. S., & de Oliveira, R. M. W. (2017). Cannabidiol reduces neuroinflammation and promotes neuroplasticity and functional recovery after brain ischemia. *Prog Neuropsychopharmacol Biol Psychiatry*, *75*, 94-105. https://doi.org/10.1016/j.pnpbp.2016.11.005

Mörs, K., Braun, O., Wagner, N., Auner, B., Voth, M., Störmann, P., Wutzler, S., Marzi, I., & Relja, B. (2016). Influence of gender on systemic il-6 levels, complication rates and outcome after major trauma. *Immunobiology*, *221*(8), 904-910. https://doi.org/10.1016/j.imbio.2016.03.005

Mosser, D. M., & Edwards, J. P. (2008). Exploring the full spectrum of macrophage activation. *Nature Reviews Immunology*, *8*(12), 958-969. https://doi.org/10.1038/nri2448

Moy, M. L., Teylan, M., Weston, N. A., Gagnon, D. R., Danilack, V. A., & Garshick, E. (2014). Daily step count is associated with plasma c-reactive protein and il-6 in a us cohort with copd. *Chest*, *145*(3), 542-550. https://doi.org/10.1378/chest.13-1052

Munro, S., Thomas, K. L., & Abu-Shaar, M. (1993). Molecular characterization of a peripheral receptor for cannabinoids. *Nature*, *365*(6441), 61. https://doi.org/10.1038/365061a0

Murphy, K., & Weaver, C. (2017). *Janeway's immunobiology* (9th ed.). Garland Science/Taylor & Francis.

Muthumalage, T., & Rahman, I. (2019). Cannabidiol differentially regulates basal and lps-induced inflammatory responses in macrophages, lung epithelial cells, and fibroblasts. *Toxicology and Applied Pharmacology, 382*, 114713. https://doi.org/10.1016/j.taap.2019.114713

Nadulski, T., Pragst, F., Weinberg, G., Roser, P., Schnelle, M., Fronk, E.-M., & Stadelmann, A. M. (2005). Randomized, double-blind, placebo-controlled study about the effects of cannabidiol (cbd) on the pharmacokinetics of δ9-tetrahydrocannabinol (thc) after oral application of thc verses standardized cannabis extract. *Therapeutic Drug Monitoring*, *27*(6), 799-810. https://doi.org/10.1097/01.ftd.0000177223.19294.5c

Naftali, T., Mechulam, R., Marii, A., Gabay, G., Stein, A., Bronshtain, M., Laish, I., Benjaminov, F., & Konikoff, F. M. (2017). Low-dose cannabidiol is safe but not effective in the treatment for crohn's disease, a randomized controlled trial. *Digestive Diseases and Sciences*, *62*(6), 1615-1620. https://doi.org/10.1007/s10620-017-4540-z

Nasreddine, Z. S., Phillips, N. A., Bédirian, V., Charbonneau, S., Whitehead, V., Collin, I., Cummings, J. L., & Chertkow, H. (2005). The montreal cognitive assessment, moca: A brief screening tool for mild cognitive impairment. *J Am Geriatr Soc*, *53*(4), 695-699. https://doi.org/10.1111/j.1532-5415.2005.53221.x

Navarrete, F., García-Gutiérrez, M. S., Jurado-Barba, R., Rubio, G., Gasparyan, A., Austrich-Olivares, A., & Manzanares, J. (2020). Endocannabinoid system components as potential biomarkers in psychiatry. *Frontiers in Psychiatry*, *11*, 315. https://doi.org/10.3389/fpsyt.2020.00315

Nishida, Y., Higaki, Y., Taguchi, N., Hara, M., Nakamura, K., Nanri, H., Imaizumi, T., Sakamoto, T., Horita, M., Shinchi, K., & Tanaka, K. (2014). Objectively measured physical activity and inflammatory cytokine levels in middle-aged japanese people. *Preventive Medicine, 64*, 81-87. https://doi.org/10.1016/j.ypmed.2014.04.004

Nofuji, Y., Suwa, M., Moriyama, Y., Nakano, H., Ichimiya, A., Nishichi, R., Sasaki, H., Radak, Z., & Kumagai, S. (2008). Decreased serum brain-derived neurotrophic factor in trained men. *Neuroscience Letters*, *437*(1), 29-32. https://doi.org/10.1016/j.neulet.2008.03.057

Norden, D. M., Trojanowski, P. J., Villanueva, E., Navarro, E., & Godbout, J. P. (2016). Sequential activation of microglia and astrocyte cytokine expression precedes increased iba-1 or gfap immunoreactivity following systemic immune challenge. *Glia*, *64*(2), 300-316. https://doi.org/10.1002/glia.22930

Nygaard, H., Falch, G. S., Whist, J. E., Hollan, I., Ellefsen, S., Holmboe-Ottesen, G., Rønnestad, B. R., & Høstmark, A. T. (2017). Acute effects of post-absorptive and postprandial moderate exercise on markers of inflammation in hyperglycemic individuals. *European Journal of Applied Physiology*, *117*(4), 787-794. https://doi.org/10.1007/s00421-017-3576-2

Oberbach, A., Lehmann, S., Kirsch, K., Krist, J., Sonnabend, M., Linke, A., Tönjes, A., Stumvoll, M., Blüher, M., & Kovacs, P. (2008). Long-term exercise training decreases interleukin-6 (il-6) serum levels in subjects with impaired glucose tolerance: Effect of the -174g/c variant in il-6 gene. *European Journal of Endocrinology*, *159*(2), 129-136. https://doi.org/10.1530/eje-08-0220

O'Callaghan, A., Harvey, M., Houghton, D., Gray, W. K., Weston, K. L., Oates, L. L., Romano, B., & Walker, R. W. (2020). Comparing the influence of exercise intensity on brain-derived neurotrophic factor serum levels in people with parkinson's disease: A pilot study. *Aging - Clinical and Experimental Research*, *32*(9), 1731-1738. https://doi.org/10.1007/s40520-019-01353-w

Osborne, A. L., Solowij, N., Babic, I., Huang, X.-F., & Weston-Green, K. (2017). Improved social interaction, recognition and working memory with cannabidiol treatment in a prenatal infection (poly i:C) rat model. *Neuropsychopharmacology*, *42*(7), 1447-1457. https://doi.org/10.1038/npp.2017.40

Osborne, A. L., Solowij, N., Babic, I., Lum, J. S., Huang, X. F., Newell, K. A., & Weston-Green, K. (2019). Cannabidiol improves behavioural and neurochemical deficits in adult female offspring of the maternal immune activation (poly i:C) model of neurodevelopmental disorders. *Brain Behav Immun, 81*, 574-587. https://doi.org/10.1016/j.bbi.2019.07.018

Osborne, A. L., Solowij, N., & Weston-Green, K. (2017). A systematic review of the effect of cannabidiol on cognitive function: Relevance to schizophrenia. *Neuroscience & Biobehavioral Reviews, 72*, 310-324. https://doi.org/10.1016/j.neubiorev.2016.11.012

Ostrowski, K., Rohde, T., Asp, S., Schjerling, P., & Pedersen, B. K. (1999). Pro- and anti-inflammatory cytokine balance in strenuous exercise in humans. *Journal of Physiology, 515 (*287-291. https://doi.org/10.1111/j.1469-7793.1999.287ad.x

Paller, C. J., Campbell, C. M., Edwards, R. R., & Dobs, A. S. (2009). Sex-based differences in pain perception and treatment. *Pain Medicine, 10*(2), 289-299. https://doi.org/10.1111/j.1526-4637.2008.00558.x

Pan, W., Banks, W. A., Fasold, M. B., Bluth, J., & Kastin, A. J. (1998). Transport of brain-derived neurotrophic factor across the blood-brain barrier. *Neuropharmacology, 37*(12), 1553-1561. https://doi.org/10.1016/s0028-3908(98)00141-5

Parbo, P., Ismail, R., Hansen, K. V., Amidi, A., Mårup, F. H., Gottrup, H., Brændgaard, H., Eriksson, B. O., Eskildsen, S. F., & Lund, T. E. (2017). Brain inflammation accompanies amyloid in the majority of mild cognitive impairment cases due to alzheimer's disease. *Brain*, *140*(7), 2002-2011.

Parray, H. A., & Yun, J. W. (2016). Cannabidiol promotes browning in 3t3-l1 adipocytes. *Molecular and Cellular Biochemistry*, *416*(1-2), 131-139. https://doi.org/10.1007/s11010-016-2702-5

Patanella, A. K., Zinno, M., Quaranta, D., Nociti, V., Frisullo, G., Gainotti, G., Tonali, P. A., Batocchi, A. P., & Marra, C. (2010). Correlations between peripheral blood mononuclear cell production of bdnf, tnf-alpha, il-6, il-10 and cognitive performances in multiple sclerosis patients. *Journal of Neuroscience Research*, *88*(5), 1106-1112. https://doi.org/10.1002/jnr.22276

Patas, K., Penninx, B. W., Bus, B. A., Vogelzangs, N., Molendijk, M. L., Elzinga, B. M., Bosker, F. J., & Oude Voshaar, R. C. (2014). Association between serum brain-derived neurotrophic factor and plasma interleukin-6 in major depressive disorder with melancholic features. *Brain Behav Immun*, *36*, 71-79. https://doi.org/10.1016/j.bbi.2013.10.007

Pedersen, B. K., & Febbraio, M. A. (2012). Muscles, exercise and obesity: Skeletal muscle as a secretory organ. *Nature Reviews Endocrinology*, *8*(8), 457-465. https://doi.org/10.1038/nrendo.2012.49

Peres, F. F., Lima, A. C., Hallak, J. E. C., Crippa, J. A., Silva, R. H., & Abílio, V. C. (2018). Cannabidiol as a promising strategy to treat and prevent movement disorders? *Frontiers in Pharmacology, 9*, 482-482. https://doi.org/10.3389/fphar.2018.00482

Perez, J. A. (2012). Gender difference in psychological well-being among filipino college student samples. *International Journal of Humanities and Social Science, 2*(13), 84-93.

Perrin, J. S., Hervé, P.-Y., Leonard, G., Perron, M., Pike, G. B., Pitiot, A., Richer, L., Veillette, S., Pausova, Z., & Paus, T. (2008). Growth of white matter in the adolescent brain: Role of testosterone and androgen receptor. *Journal of Neuroscience, 28*(38), 9519-9524. https://doi.org/10.1523/jneurosci.1212-08.2008

Pertwee, R. G. (1997). Pharmacology of cannabinoid cb1 and cb2 receptors. *Pharmacology & Therapeutics*, *74*(2), 129-180. https://doi.org/https://doi.org/10.1016/S0163-7258(97)82001-3

Pescatello, L., Arena, R., Riebe, D., & Thompson, P. (2014). Health-related physical fitness testing and interpretation. In *Acsm's guidelines for exercise testing and prescription* (9 ed., pp. 73-76). Wolters Kluwer/Lippincott Williams & Wilkins.

Petersen, A. M., & Pedersen, B. K. (2005). The anti-inflammatory effect of exercise. *Journal of Applied Physiology, 98*(4), 1154-1162. https://doi.org/10.1152/japplphysiol.00164.2004

Petrosino, S., Verde, R., Vaia, M., Allarà, M., Iuvone, T., & Di Marzo, V. (2018). Anti-inflammatory properties of cannabidiol, a nonpsychotropic cannabinoid, in experimental allergic contact dermatitis. *Journal of Pharmacology and Experimental Therapeutics*, *365*(3), 652-663. https://doi.org/10.1124/jpet.117.244368

Pfefferbaum, B., & North, C. S. (2020). Mental health and the covid-19 pandemic. *New England Journal of Medicine*, *383*(6), 510-512. https://doi.org/10.1056/NEJMp2008017

Pischon, T., Hankinson, S. E., Hotamisligil, G. S., Rifai, N., & Rimm, E. B. (2003). Leisure-time physical activity and reduced plasma levels of obesity-related inflammatory markers. *Obesity Research*, *11*(9), 1055-1064. https://doi.org/10.1038/oby.2003.145

Pollock, M. L., Bohannon, R. L., Cooper, K. H., Ayres, J. J., Ward, A., White, S. R., & Linnerud, A. C. (1976). A comparative analysis of four protocols for maximal treadmill stress testing. *American Heart Journal*, *92*(1), 39-46. https://doi.org/10.1016/s0002-8703(76)80401-2

Prather, A. A., Carroll, J. E., Fury, J. M., McDade, K. K., Ross, D., & Marsland, A. L. (2009). Gender differences in stimulated cytokine production following acute psychological stress. *Brain Behav Immun*, *23*(5), 622-628. https://doi.org/https://doi.org/10.1016/j.bbi.2008.11.004

Premoli, M., Aria, F., Bonini, S. A., Maccarinelli, G., Gianoncelli, A., Pina, S. D., Tambaro, S., Memo, M., & Mastinu, A. (2019). Cannabidiol: Recent advances and new insights for neuropsychiatric disorders treatment. *Life Sci*, *224*, 120-127. https://doi.org/10.1016/j.lfs.2019.03.053

Radin, D. P., & Patel, P. (2017). Bdnf: An oncogene or tumor suppressor? *Anticancer Research*, *37*(8), 3983-3990. https://doi.org/10.21873/anticanres.11783

Ramos-Arellano, L. E., Matia-Garcia, I., Marino-Ortega, L. A., Castro-Alarcón, N., Muñoz-Valle, J. F., Salgado-Goytia, L., Salgado-Bernabé, A. B., & Parra-Rojas, I. (2020). Obesity, dyslipidemia, and high blood pressure are associated with cardiovascular risk, determined using high-sensitivity c-reactive protein concentration, in young adults. *Journal of International Medical Research*, *48*(12), 300060520980596. https://doi.org/10.1177/0300060520980596

Rasmussen, P., Brassard, P., Adser, H., Pedersen, M. V., Leick, L., Hart, E., Secher, N. H., Pedersen, B. K., & Pilegaard, H. (2009). Evidence for a release of brain-derived neurotrophic factor from the brain during exercise. *Experimental Physiology, 94*(10), 1062-1069. https://doi.org/10.1113/expphysiol.2009.048512

Renaud, A. M., & Cormier, Y. (1986). Acute effects of marihuana smoking on maximal exercise performance. *Medicine and Science in Sports and Exercise, 18*(6), 685-689. https://pubmed.ncbi.nlm.nih.gov/3097453/

Renault, K., Carlsen, E., Haedersdal, S., Nilas, L., Secher, N., Eugen-Olsen, J., Cortes, D., Olsen, S., Halldorsson, T., & Nørgaard, K. (2017). Impact of lifestyle intervention for obese women during pregnancy on maternal metabolic and inflammatory markers. *International journal of obesity, 41*(4), 598-605. https://doi.org/10.1038/ijo.2017.9

Reuben, D. B., Judd-Hamilton, L., Harris, T. B., & Seeman, T. E. (2003). The associations between physical activity and inflammatory markers in high-functioning older persons: Macarthur studies of successful aging. *J Am Geriatr Soc, 51*(8), 1125-1130. https://doi.org/10.1046/j.1532-5415.2003.51380.x

Rexrode, K. M., Pradhan, A., Manson, J. E., Buring, J. E., & Ridker, P. M. (2003). Relationship of total and abdominal adiposity with crp and il-6 in women. *Annals of epidemiology, 13*(10), 674-682. https://doi.org/10.1016/s1047-2797(03)00053-x

Ribeiro, A., Almeida, V., Costola-de-Souza, C., Ferraz-de-Paula, V., Pinheiro, M., Vitoretti, L., Gimenes-Junior, J., Akamine, A., Crippa, J., & Tavares-de-Lima, W. (2015). Cannabidiol improves lung function and inflammation in mice submitted to lps-induced acute lung injury. *Immunopharmacology and Immunotoxicology, 37*(1), 35-41. https://doi.org/10.3109/08923973.2014.976794

Ribeiro, A., Ferraz-de-Paula, V., Pinheiro, M. L., Vitoretti, L. B., Mariano-Souza, D. P., Quinteiro-Filho, W. M., Akamine, A. T., Almeida, V. I., Quevedo, J., & Dal-Pizzol, F. (2012). Cannabidiol, a non-psychotropic plant-derived cannabinoid, decreases inflammation in a murine model of acute lung injury: Role for the adenosine a2a receptor. *European Journal of Pharmacology*, *678*(1-3), 78-85. https://doi.org/10.1016/j.ejphar.2011.12.043

Ridker, P. M. (2003). Clinical application of c-reactive protein for cardiovascular disease detection and prevention. *Circulation*, *107*(3), 363-369. https://doi.org/10.1161/01.cir.0000053730.47739.3c

Riebe, C. J. N., Hill, M. N., Lee, T. T. Y., Hillard, C. J., & Gorzalka, B. B. (2010). Estrogenic regulation of limbic cannabinoid receptor binding. *Psychoneuroendocrinology*, *35*(8), 1265-1269. https://doi.org/https://doi.org/10.1016/j.psyneuen.2010.02.008

Riebe, D., Ehrman, J., Liguori, G., & Magal, M. (2018). *Acsm's guidelines for exercise testing and prescription* (10 ed.). Wolters Kluwer.

Riecher-Rössler, A. (2017). Sex and gender differences in mental disorders. *Lancet Psychiatry*, *4*(1), 8-9. https://doi.org/10.1016/s2215-0366(16)30348-0

Robbins, T. W. (2011). Cognition: The ultimate brain function. *Neuropsychopharmacology*, *36*(1), 1-2. https://doi.org/10.1038/npp.2010.171

Rothrock, N. E., Amtmann, D., & Cook, K. F. (2020). Development and validation of an interpretive guide for promis scores. *Journal of Patient-Reported Outcomes*, *4*(1), 16. https://doi.org/10.1186/s41687-020-0181-7

Ruehle, S., Rey, A. A., Remmers, F., & Lutz, B. (2012). The endocannabinoid system in anxiety, fear memory and habituation. *Journal of Psychopharmacology*, *26*(1), 23-39. https://doi.org/10.1177/0269881111408958

Ryff, C. D., & Keyes, C. L. M. (1995). The structure of psychological well-being revisited. *Journal of Personality and Social Psychology*, *69*(4), 719. https://doi.org/10.1037//0022-3514.69.4.719

Saffer, B. Y., Lanting, S. C., Koehle, M. S., Klonsky, E. D., & Iverson, G. L. (2015). Assessing cognitive impairment using promis(®) applied cognition-abilities scales in a medical outpatient sample. *Psychiatry Research*, *226*(1), 169-172. https://doi.org/10.1016/j.psychres.2014.12.043

Sahinovic, A., Irwin, C., Doohan, P. T., Kevin, R. C., Cox, A. J., Lau, N. S., Desbrow, B., Johnson, N. A., Sabag, A., & Hislop, M. (2022). Effects of cannabidiol on exercise physiology and bioenergetics: A randomised controlled pilot trial. *Sports Medicine - Open*, *8*(1), 1-18. https://doi.org/10.1186/s40798-022-00417-y

Sales, A. J., Fogaça, M. V., Sartim, A. G., Pereira, V. S., Wegener, G., Guimarães, F. S., & Joca, S. R. L. (2019). Cannabidiol induces rapid and sustained antidepressant-like effects through increased bdnf signaling and synaptogenesis in the prefrontal cortex. *Mol Neurobiol*, *56*(2), 1070-1081. https://doi.org/10.1007/s12035-018-1143-4

Sales, A. J., Guimarães, F. S., & Joca, S. R. L. (2020). Cbd modulates DNA methylation in the prefrontal cortex and hippocampus of mice exposed to forced swim. *Behavioural Brain Research*, *388*, 112627. https://doi.org/10.1016/j.bbr.2020.112627

Sardeli, A. V., Tomeleri, C. M., Cyrino, E. S., Fernhall, B., Cavaglieri, C. R., & Chacon-Mikahil, M. P. T. (2018). Effect of resistance training on inflammatory markers of older adults: A meta-analysis. *Experimental Gerontology, 111*, 188-196. https://doi.org/10.1016/j.exger.2018.07.021

Sartim, A. G., Guimarães, F. S., & Joca, S. R. L. (2016). Antidepressant-like effect of cannabidiol injection into the ventral medial prefrontal cortex—possible involvement of 5-ht1a and cb1 receptors. *Behavioural Brain Research, 303*, 218-227. https://doi.org/10.1016/j.bbr.2016.01.033

Scharfman, H. E., Goodman, J. H., & Sollas, A. L. (1999). Actions of brain-derived neurotrophic factor in slices from rats with spontaneous seizures and mossy fiber sprouting in the dentate gyrus. *Journal of Neuroscience, 19*(13), 5619-5631. https://doi.org/10.1523/jneurosci.19-13-05619.1999

Scharfman, H. E., & MacLusky, N. J. (2006). Estrogen and brain-derived neurotrophic factor (bdnf) in hippocampus: Complexity of steroid hormone-growth factor interactions in the adult cns. *Frontiers in Neuroendocrinology, 27*(4), 415-435. https://doi.org/10.1016/j.yfrne.2006.09.004

Schiavon, A. P., Bonato, J. M., Milani, H., Guimarães, F. S., & Weffort de Oliveira, R. M. (2016). Influence of single and repeated cannabidiol administration on emotional behavior and markers of cell proliferation and neurogenesis in non-stressed mice. *Prog Neuropsychopharmacol Biol Psychiatry, 64*, 27-34. https://doi.org/10.1016/j.pnpbp.2015.06.017

Schiffer, T., Schulte, S., Hollmann, W., Bloch, W., & Strüder, H. K. (2009). Effects of strength and endurance training on brain-derived neurotrophic factor and insulin-like growth factor 1 in humans. *Hormone and Metabolic Research, 41*(3), 250-254. https://doi.org/10.1055/s-0028-1093322

Schindler, R., Mancilla, J., Endres, S., Ghorbani, R., Clark, S. C., & Dinarello, C. A. (1990). Correlations and interactions in the production of interleukin-6 (il-6), il-1, and tumor necrosis factor (tnf) in human blood mononuclear cells: Il-6 suppresses il-1 and tnf. *Blood, 75*(1), 40-47. https://doi.org/10.1182/blood.V75.1.40.40

Schoedel, K. A., Szeto, I., Setnik, B., Sellers, E. M., Levy-Cooperman, N., Mills, C., Etges, T., & Sommerville, K. (2018). Abuse potential assessment of cannabidiol (cbd) in recreational polydrug users: A randomized, double-blind, controlled trial. *Epilepsy & Behavior 88*, 162-171. https://doi.org/10.1016/j.yebeh.2018.07.027

Schräder, N. H. B., Duipmans, J. C., Molenbuur, B., Wolff, A. P., & Jonkman, M. F. (2019). Combined tetrahydrocannabinol and cannabidiol to treat pain in epidermolysis bullosa: A report of three cases. *Epilepsy & Behavior, 180*(4), 922-924. https://doi.org/10.1111/bjd.17341

Schulz, P., Hryhorowicz, S., Rychter, A. M., Zawada, A., Słomski, R., Dobrowolska, A., & Krela-Kaźmierczak, I. (2021). What role does the endocannabinoid system play in the pathogenesis of obesity? *Nutrients, 13*(2), 373.

Sember, V., Meh, K., Sorić, M., Starc, G., Rocha, P., & Jurak, G. (2020). Validity and reliability of the ipaq for adults across eu countries: Systematic review and meta analysis. *International Journal of Environmental Research and Public Health, 17*(19). https://doi.org/10.3390/ijerph17197161

Seo, D. I., Kim, E., Fahs, C. A., Rossow, L., Young, K., Ferguson, S. L., Thiebaud, R., Sherk, V. D., Loenneke, J. P., Kim, D., Lee, M. K., Choi, K. H., Bemben, D. A., Bemben, M. G., & So, W. Y. (2012). Reliability of the one-repetition maximum test based on muscle group and gender. *Journal of Sports Science and Medicine*, *11*(2), 221-225. https://pubmed.ncbi.nlm.nih.gov/24149193/

Shannon, S., Lewis, N., Lee, H., & Hughes, S. (2019). Cannabidiol in anxiety and sleep: A large case series. *Permanente Journal*, *23*, 18-041. https://doi.org/10.7812/TPP/18-041

Shbiro, L., Hen-Shoval, D., Hazut, N., Rapps, K., Dar, S., Zalsman, G., Mechoulam, R., Weller, A., & Shoval, G. (2019). Effects of cannabidiol in males and females in two different rat models of depression. *Physiology & Behavior*, *201*, 59-63. https://doi.org/10.1016/j.physbeh.2018.12.019

Shoval, G., & Weizman, A. (2005). The possible role of neurotrophins in the pathogenesis and therapy of schizophrenia. *European College of Neuropsychopharmacology*, *15*(3), 319-329. https://doi.org/10.1016/j.euroneuro.2004.12.005

Silote, G., Reinert, L., Hasselstrøm, J., Joca, S., & Wegener, G. (2020). P. 212 cannabidiol effect on genes related to bdnf-trkb and glutamatergic neurotransmission in the flinders sensitive line rat. *European Neuropsychopharmacology*, *31*(1), S27-S28. https://doi.org/10.1016/j.euroneuro.2019.12.038

Silote, G. P., Sartim, A., Sales, A., Eskelund, A., Guimaraes, F. S., Wegener, G., & Joca, S. (2019). Emerging evidence for the antidepressant effect of cannabidiol and the underlying molecular mechanisms. *J Chem Neuroanat*, *98*, 104-116. https://doi.org/10.1016/j.jchemneu.2019.04.006

Silva, G. D., Del Guerra, F. B., de Oliveira Lelis, M., & Pinto, L. F. (2020). Cannabidiol in the treatment of epilepsy: A focused review of evidence and gaps. *Front Neurol, 11*, 531939. https://doi.org/10.3389/fneur.2020.531939

Skriver, K., Roig, M., Lundbye-Jensen, J., Pingel, J., Helge, J. W., Kiens, B., & Nielsen, J. B. (2014). Acute exercise improves motor memory: Exploring potential biomarkers. *Neurobiology of Learning and Memory*, *116*, 46-58. https://doi.org/10.1016/j.nlm.2014.08.004

Smith, J. K., Dykes, R., Douglas, J. E., Krishnaswamy, G., & Berk, S. (1999). Long-term exercise and atherogenic activity of blood mononuclear cells in persons at risk of developing ischemic heart disease. *JAMA, 281*(18), 1722-1727. https://doi.org/10.1001/jama.281.18.1722

Sohrabji, F., & Lewis, D. K. (2006). Estrogen–bdnf interactions: Implications for neurodegenerative diseases. *Frontiers in Neuroendocrinology*, *27*(4), 404-414. https://doi.org/10.1016/j.yfrne.2006.09.003

Sokka, T., & Pincus, T. (2009). Erythrocyte sedimentation rate, c-reactive protein, or rheumatoid factor are normal at presentation in 35%–45% of patients with rheumatoid arthritis seen between 1980 and 2004: Analyses from finland and the united states. *Journal of Rheumatology*, *36*(7), 1387. https://doi.org/10.3899/jrheum.080770

Solowij, N., Broyd, S. J., Beale, C., Prick, J. A., Greenwood, L. M., van Hell, H., Suo, C., Galettis, P., Pai, N., Fu, S., Croft, R. J., Martin, J. H., & Yucel, M. (2018). Therapeutic effects of prolonged cannabidiol treatment on psychological symptoms and cognitive function in regular cannabis users: A pragmatic open-label clinical trial. *Cannabis Cannabinoid Res*, *3*(1), 21-34. https://doi.org/10.1089/can.2017.0043

Spillane, J., & McAllister, W. B. (2003). Keeping the lid on: A century of drug regulation and control. *Drug and Alcohol Dependence*, *70*(3 Suppl), S5-12. https://doi.org/10.1016/s0376-8716(03)00096-6

Spindle, T. R., Cone, E. J., Goffi, E., Weerts, E. M., Mitchell, J. M., Winecker, R. E., Bigelow, G. E., Flegel, R. R., & Vandrey, R. (2020). Pharmacodynamic effects of vaporized and oral cannabidiol (cbd) and vaporized cbd-dominant cannabis in infrequent cannabis users. *Drug and Alcohol Dependence*, *211*, 107937. https://doi.org/10.1016/j.drugalcdep.2020.107937

Sproston, N. R., & Ashworth, J. J. (2018). Role of c-reactive protein at sites of inflammation and infection. *Frontiers in Immunology*, *9*, 754. https://doi.org/10.3389/fimmu.2018.00754

Steadward, R. D., & Singh, M. (1975). The effects of smoking marihuana on physical performance. *Medicine and Science in Sports*, *7*(4), 309-311. https://pubmed.ncbi.nlm.nih.gov/1235156/

Steensberg, A., Fischer, C. P., Keller, C., Møller, K., & Pedersen, B. K. (2003). Il-6 enhances plasma il-1ra, il-10, and cortisol in humans. *American Journal of Physiology - Endocrinology and Metabolism*, *285*(2), E433-E437. https://doi.org/10.1152/ajpendo.00074.2003

Stempel, A. V., Stumpf, A., Zhang, H. Y., Özdoğan, T., Pannasch, U., Theis, A. K., Otte, D. M., Wojtalla, A., Rácz, I., Ponomarenko, A., Xi, Z. X., Zimmer, A., & Schmitz, D. (2016). Cannabinoid type 2 receptors mediate a cell type-specific plasticity in the hippocampus. *Neuron*, *90*(4), 795-809. https://doi.org/10.1016/j.neuron.2016.03.034

Steptoe, A., Owen, N., Kunz-Ebrecht, S., & Mohamed-Ali, V. (2002). Inflammatory cytokines, socioeconomic status, and acute stress responsivity. *Brain Behav Immun*, *16*(6), 774-784. https://doi.org/10.1016/S0889-1591(02)00030-2

Stetz, M. C., Thomas, M. L., Russo, M. B., Stetz, T. A., Wildzunas, R. M., McDonald, J. J., Wiederhold, B. K., & Romano, J. A. (2007). Stress, mental health, and cognition: A brief review of relationships and countermeasures. *Aviation, Space, and Environmental Medicine*, *78*(5), B252-B260.

Stewart, L. K., Flynn, M. G., Campbell, W. W., Craig, B. A., Robinson, J. P., Timmerman, K. L., McFarlin, B. K., Coen, P. M., & Talbert, E. (2007). The influence of exercise training on inflammatory cytokines and c-reactive protein. *Medicine and Science in Sports and Exercise*, *39*(10), 1714. https://doi.org/10.1249/mss.0b013e31811ece1c

St. Pierre Schneider, B., Correia, L. A., & Cannon, J. G. (1999). Sex differences in leukocyte invasion in injured murine skeletal muscle. *Research in Nursing & Health*, *22*(3), 243-250. https://doi.org/10.1002/(sici)1098-240x(199906)22:3<243::aid-nur6>3.0.co;2-x

Stupka, N., Lowther, S., Chorneyko, K., Bourgeois, J., Hogben, C., & Tarnopolsky, M. (2000). Gender differences in muscle inflammation after eccentric exercise. *Journal of Applied Physiology*, *89*(6), 2325-2332. https://doi.org/10.1152/jappl.2000.89.6.2325

Su, Q., Cheng, Y., Jin, K., Cheng, J., Lin, Y., Lin, Z., Wang, L., & Shao, B. (2016). Estrogen therapy increases bdnf expression and improves post-stroke depression in ovariectomy-treated rats. *Experimental and Therapeutic Medicine*, *12*(3), 1843-1848. https://doi.org/10.3892/etm.2016.3531

Sugiura, T., Kobayashi, Y., Oka, S., & Waku, K. (2002). Biosynthesis and degradation of anandamide and 2-arachidonoylglycerol and their possible physiological significance. *Prostaglandins, Leukotrienes & Essential Fatty Acids*, *66*(2-3), 173-192. https://doi.org/10.1054/plef.2001.0356

Sultan, S. R., O'Sullivan, S. E., & England, T. J. (2020). The effects of acute and sustained cannabidiol dosing for seven days on the haemodynamics in healthy men: A randomised controlled trial. *Br J Clin Pharmacol*, *86*(6), 1125-1138. https://doi.org/10.1111/bcp.14225

Sung, Y. H., Kim, S. C., Hong, H. P., Park, C. Y., Shin, M. S., Kim, C. J., Seo, J. H., Kim, D. Y., Kim, D. J., & Cho, H. J. (2012). Treadmill exercise ameliorates dopaminergic neuronal loss through suppressing microglial activation in parkinson's disease mice. *Life Sci*, *91*(25-26), 1309-1316. https://doi.org/10.1016/j.lfs.2012.10.003

Szuhany, K. L., & Otto, M. W. (2020). Assessing bdnf as a mediator of the effects of exercise on depression. *Journal of Psychiatric Research*, *123*, 114-118. https://doi.org/10.1016/j.jpsychires.2020.02.003

Taaffe, D. R., Harris, T. B., Ferrucci, L., Rowe, J., & Seeman, T. E. (2000). Cross-sectional and prospective relationships of interleukin-6 and c-reactive protein with physical performance in elderly persons: Macarthur studies of successful aging. *Journals of Gerontology Series A Biological Sciences and Medical Sciences*, *55*(12), M709-M715. https://doi.org/10.1093/gerona/55.12.m709

Terlizzi, E. P., & Norris, T. (2021, Oct). *Mental health treatment among adults: United states, 2020*. Centers for Disease Control and Prevention. https://www.cdc.gov/nchs/products/databriefs/db419.htm

Tesema, G., George, M., Hadgu, A., Haregot, E., Mondal, S., & Mathivana, D. (2019). Does chronic high-intensity endurance training have an effect on cardiovascular markers of active populations and athletes? Systematic review and meta-analysis. *BMJ Open*, *9*(10), e032832. https://doi.org/10.1136/bmjopen-2019-032832

Tham, M., Yilmaz, O., Alaverdashvili, M., Kelly, M. E., Denovan-Wright, E. M., & Laprairie, R. B. (2019). Allosteric and orthosteric pharmacology of cannabidiol and cannabidiol-dimethylheptyl at the type 1 and type 2 cannabinoid receptors. *Br J Pharmacol*, *176*(10), 1455-1469. https://doi.org/10.1111/bph.14440

Thomas, K., & Davies, A. (2005). Neurotrophins: A ticket to ride for bdnf. *Current Biology*, *15*(7), R262-R264. https://doi.org/https://doi.org/10.1016/j.cub.2005.03.023

Thompson, D., Pepys, M. B., & Wood, S. P. (1999). The physiological structure of human c-reactive protein and its complex with phosphocholine. *Structure*, *7*(2), 169-177. https://doi.org/10.1016/S0969-2126(99)80023-9

Thorand, B., Baumert, J., Döring, A., Herder, C., Kolb, H., Rathmann, W., Giani, G., & Koenig, W. (2006). Sex differences in the relation of body composition to markers of inflammation. *Atherosclerosis*, *184*(1), 216-224. https://doi.org/10.1016/j.atherosclerosis.2005.04.011

Timmons, B. W., Hamadeh, M. J., Devries, M. C., & Tarnopolsky, M. A. (2005). Influence of gender, menstrual phase, and oral contraceptive use on immunological changes in response to prolonged cycling. *Journal of Applied Physiology*, *99*(3), 979-985. https://doi.org/10.1152/japplphysiol.00171.2005

Timmons, B. W., Hamadeh, M. J., & Tarnopolsky, M. A. (2006). No effect of short-term 17β-estradiol supplementation in healthy men on systemic inflammatory responses to exercise. *American Journal of Physiology-Regulatory, Integrative and Comparative Physiology, 291*(2), R285-R290. https://doi.org/10.1152/ajpregu.00605.2005

Timmons, B. W., Tarnopolsky, M. A., Snider, D. P., & Bar-Or, O. (2006). Immunological changes in response to exercise: Influence of age, puberty, and gender. *Medicine and Science in Sports and Exercise 38*(2), 293-304. https://doi.org/10.1249/01.mss.0000183479.90501.a0

Timmusk, T., Palm, K., Metsis, M., Reintam, T., Paalme, V., Saarma, M., & Persson, H. (1993). Multiple promoters direct tissue-specific expression of the rat bdnf gene. *Neuron, 10*(3), 475-489. https://doi.org/10.1016/0896-6273(93)90335-o

Toll, A., Berge, D., Burling, K., Scoriels, L., Treen, D., Monserrat, C., Marmol, F., Duran, X., Jones, P. B., Perez-Sola, V., Fernandez-Egea, E., & Mane, A. (2020). Cannabis use influence on peripheral brain-derived neurotrophic factor levels in antipsychotic-naive first-episode psychosis. *European Archives of Psychiatry and Clinical Neuroscience, 270*(7), 851-858. https://doi.org/10.1007/s00406-020-01117-y

Toran-Allerand, C. D. (2004). Minireview: A plethora of estrogen receptors in the brain: Where will it end? *Endocrinology, 145*(3), 1069-1074.

Trajkovska, V., Marcussen, A. B., Vinberg, M., Hartvig, P., Aznar, S., & Knudsen, G. M. (2007). Measurements of brain-derived neurotrophic factor: Methodological aspects and demographical data. *Brain Research Bulletin, 73*(1-3), 143-149. https://doi.org/10.1016/j.brainresbull.2007.03.009

Tsai, C. L., Pai, M. C., Ukropec, J., & Ukropcová, B. (2019). Distinctive effects of aerobic and resistance exercise modes on neurocognitive and biochemical changes in individuals with mild cognitive impairment. *Curr Alzheimer Res*, *16*(4), 316-332. https://doi.org/10.2174/1567205016666190228125429

Tsalik, E. L., Jaggers, L. B., Glickman, S. W., Langley, R. J., van Velkinburgh, J. C., Park, L. P., Fowler, V. G., Cairns, C. B., Kingsmore, S. F., & Woods, C. W. (2012). Discriminative value of inflammatory biomarkers for suspected sepsis. *Journal of Emergency Medicine*, *43*(1), 97-106. https://doi.org/10.1016/j.jemermed.2011.05.072

Tudor-Locke, C., & Bassett, D. R. (2004). How many steps/day are enough? *Sports Medicine*, *34*(1), 1-8. https://doi.org/10.1186/1479-5868-8-79

Tudor-Locke, C., Johnson, W. D., & Katzmarzyk, P. T. (2009). Accelerometer-determined steps per day in us adults. *Medicine and Science in Sports and Exercise*, *41*(7), 1384-1391. https://doi.org/10.1249/MSS.0b013e318199885c

Tudor-Locke, C., Leonardi, C., Johnson, W. D., Katzmarzyk, P. T., & Church, T. S. (2011). Accelerometer steps/day translation of moderate-to-vigorous activity. *Preventive Medicine*, *53*(1-2), 31-33. https://doi.org/10.1016/j.ypmed.2011.01.014

Turcotte, C., Blanchet, M. R., Laviolette, M., & Flamand, N. (2016). The cb(2) receptor and its role as a regulator of inflammation. *Cellular and Molecular Life Sciences*, *73*(23), 4449-4470. https://doi.org/10.1007/s00018-016-2300-4

Urabe, H., Kojima, H., Chan, L., Terashima, T., Ogawa, N., Katagi, M., Fujino, K., Kumagai, A., Kawai, H., Asakawa, A., Inui, A., Yasuda, H., Eguchi, Y., Oka, K., Maegawa, H., Kashiwagi, A., & Kimura, H. (2013). Haematopoietic cells produce bdnf and regulate appetite upon migration to the hypothalamus. *Nature Communications*, *4*, 1526. https://doi.org/10.1038/ncomms2536

Vaduganathan, M., Pareek, M., Qamar, A., Pandey, A., Olsen, M. H., & Bhatt, D. L. (2018). Baseline blood pressure, the 2017 acc/aha high blood pressure guidelines, and long-term cardiovascular risk in sprint. *American Journal of Medicine*, *131*(8), 956-960. https://doi.org/10.1016/j.amjmed.2017.12.049

Valentine, T. R., Weiss, D. M., Jones, J. A., & Andersen, B. L. (2019). Construct validity of promis cognitive function in cancer patients and noncancer controls. *Health Psychology*, *38*(5), 351-358. https://doi.org/10.1037/hea0000693

Wagner, G., Herbsleb, M., Cruz, F. d. l., Schumann, A., Brünner, F., Schachtzabel, C., Gussew, A., Puta, C., Smesny, S., & Gabriel, H. W. (2015). Hippocampal structure, metabolism, and inflammatory response after a 6-week intense aerobic exercise in healthy young adults: A controlled trial. *Journal of Cerebral Blood Flow & Metabolism*, *35*(10), 1570-1578. https://doi.org/10.1038/jcbfm.2015.125

Walker, O. S., Holloway, A. C., & Raha, S. (2019). The role of the endocannabinoid system in female reproductive tissues. *Journal of Ovarian Research*, *12*(1), 3. https://doi.org/10.1186/s13048-018-0478-9

Ware, M. A., Jensen, D., Barrette, A., Vernec, A., & Derman, W. (2018). Cannabis and the health and performance of the elite athlete. *Clinical Journal of Sport Medicine*, *28*(5), 480-484. https/doi.org/10.1097/jsm.0000000000000650

Warren, S. G., Humphreys, A. G., Juraska, J. M., & Greenough, W. T. (1995). Ltp varies across the estrous cycle: Enhanced synaptic plasticity in proestrus rats. *Brain Research, 703*(1-2), 26-30. https://doi.org/10.1016/0006-8993(95)01059-9

Watanabe, S., Mu, W., Kahn, A., Jing, N., Li, J. H., Lan, H. Y., Nakagawa, T., Ohashi, R., & Johnson, R. J. (2004). Role of jak/stat pathway in il-6-induced activation of vascular smooth muscle cells. *American Journal of Nephrology, 24*(4), 387-392. https://doi.org/10.1159/000079706

Webb, M. A., Mani, H., Robertson, S. J., Waller, H. L., Webb, D. R., Edwardson, C. L., Bodicoat, D. H., Yates, T., Khunti, K., & Davies, M. J. (2018). Moderate increases in daily step count are associated with reduced il6 and crp in women with pcos. *Endocrine Connections, 7*(12), 1442-1447. https://doi.org/10.1530/ec-18-0438

Wefel, J. S., Vardy, J., Ahles, T., & Schagen, S. B. (2011). International cognition and cancer task force recommendations to harmonise studies of cognitive function in patients with cancer. *Lancet Oncology, 12*(7), 703-708. https://doi.org/10.1016/S1470-2045(10)70294-1

Wens, I., Keytsman, C., Deckx, N., Cools, N., Dalgas, U., & Eijnde, B. O. (2016). Brain derived neurotrophic factor in multiple sclerosis: Effect of 24 weeks endurance and resistance training. *European Journal of Neurology, 23*(6), 1028-1035. https://doi.org/10.1111/ene.12976

Wheeler, M., Merten, J. W., Gordon, B. T., & Hamadi, H. (2020). Cbd (cannabidiol) product attitudes, knowledge, and use among young adults. *Substance Use & Misuse, 55*(7), 1138-1145. https://doi.org/10.1080/10826084.2020.1729201

Wheeler, M. J., Green, D. J., Ellis, K. A., Cerin, E., Heinonen, I., Naylor, L. H., Larsen, R., Wennberg, P., Boraxbekk, C. J., Lewis, J., Eikelis, N., Lautenschlager, N. T., Kingwell, B. A., Lambert, G., Owen, N., & Dunstan, D. W. (2020). Distinct effects of acute exercise and breaks in sitting on working memory and executive function in older adults: A three-arm, randomised cross-over trial to evaluate the effects of exercise with and without breaks in sitting on cognition. *British Journal of Sports Medicine, 54*(13), 776-781. https://doi.org/10.1136/bjsports-2018-100168

Williams, N. N. B., Ewell, T. R., Abbotts, K. S. S., Harms, K. J., Woelfel, K. A., Dooley, G. P., Weir, T. L., & Bell, C. (2021). Comparison of five oral cannabidiol preparations in adult humans: Pharmacokinetics, body composition, and heart rate variability. *Pharmaceuticals*, *14*(1). https://doi.org/10.3390/ph14010035

Wingate, S. (1997). Cardiovascular anatomy and physiology in the female. *Critical Care Nursing Clinics of North America*, *9*(4), 447-452. https://pubmed.ncbi.nlm.nih.gov/9444167/

Wood, L. J., Nail, L. M., & Winters, K. A. (2009). Does muscle-derived interleukin-6 mediate some of the beneficial effects of exercise on cancer treatment-related fatigue? *Oncology Nursing Forum, 36*(5), 519-524. https://doi.org/10.1188/09.onf.519-524

Wright, C. E., Strike, P. C., Brydon, L., & Steptoe, A. (2005). Acute inflammation and negative mood: Mediation by cytokine activation. *Brain Behav Immun*, *19*(4), 345-350. https://doi.org/10.1016/j.bbi.2004.10.003

Yamamoto, H., & Gurney, M. E. (1990). Human platelets contain brain-derived neurotrophic factor. *Journal of Neuroscience, 10*(11), 3469-3478. https://doi.org/10.1523/jneurosci.10-11-03469.1990

Yang, L. Y., & Arnold, A. P. (2000). Interaction of bdnf and testosterone in the regulation of adult perineal motoneurons. *Journal of Neurobiology, 44*(3), 308-319. https://doi.org/10.1002/1097-4695(20000905)44:3<308::aid-neu2>3.0.co;2-m

YorkWilliams, S. L., Gust, C. J., Mueller, R., Bidwell, L. C., Hutchison, K. E., Gillman, A. S., & Bryan, A. D. (2019). The new runner's high? Examining relationships between cannabis use and exercise behavior in states with legalized cannabis. *Frontiers in Public Health, 7*, 99. https://doi.org/10.3389/fpubh.2019.00099

Zang, L., Wang, S. Q., Mao, N., Fu, X. J., Lin, X. J., Meng, D. J., & Li, G. (2019). Effect of different walking number on inflammation and nutrition in patients with chronic kidney disease. *Sichuan Da Xue Xue Bao Yi Xue Ban, 50*(2), 252-255. https://pubmed.ncbi.nlm.nih.gov/31106548/

Zatterale, F., Longo, M., Naderi, J., Raciti, G. A., Desiderio, A., Miele, C., & Beguinot, F. (2020). Chronic adipose tissue inflammation linking obesity to insulin resistance and type 2 diabetes. *Frontiers in Physiology, 10*, 1607. https://doi.org/10.3389/fphys.2019.01607

Zeiger, J. S., Silvers, W. S., Fleegler, E. M., & Zeiger, R. S. (2019). Cannabis use in active athletes: Behaviors related to subjective effects. *PLoS One, 14*(6), e0218998. https://doi.org/10.1371/journal.pone.0218998

Zhang, H. Y., Bi, G. H., Li, X., Li, J., Qu, H., Zhang, S. J., Li, C. Y., Onaivi, E. S., Gardner, E. L., Xi, Z. X., & Liu, Q. R. (2015). Species differences in cannabinoid receptor 2 and receptor responses to cocaine self-administration in mice and rats. *Neuropsychopharmacology, 40*(4), 1037-1051. https://doi.org/10.1038/npp.2014.297

Zhang, H. Y., Gao, M., Liu, Q. R., Bi, G. H., Li, X., Yang, H. J., Gardner, E. L., Wu, J., & Xi, Z. X. (2014). Cannabinoid cb2 receptors modulate midbrain dopamine neuronal activity and dopamine-related behavior in mice. *Proceedings of the National Academy of Sciences*, *111*(46), E5007-5015. https://doi.org/10.1073/pnas.1413210111

Ziegenhorn, A. A., Schulte-Herbrüggen, O., Danker-Hopfe, H., Malbranc, M., Hartung, H.-D., Anders, D., Lang, U. E., Steinhagen-Thiessen, E., Schaub, R. T., & Hellweg, R. (2007). Serum neurotrophins--a study on the time course and influencing factors in a large old age sample. *Neurobiology of Aging*, *28*(9), 1436-1445. https://doi.org/10.1016/j.neurobiolaging.2006.06.011

Zimmer, P., Baumann, F. T., Oberste, M., Schmitt, J., Joisten, N., Hartig, P., Schenk, A., Kuhn, R., Bloch, W., & Reuss-Borst, M. (2018). Influence of personalized exercise recommendations during rehabilitation on the sustainability of objectively mmeasured physical activity levels, fatigue, and fatigue-related biomarkers in patients with breast cancer. *Integrative Cancer Therapies*, *17*(2), 306-311. https://doi.org/10.1177/1534735417713301

Zoladz, J. A., Majerczak, J., Zeligowska, E., Mencel, J., Jaskolski, A., Jaskolska, A., & Marusiak, J. (2014). Moderate-intensity interval training increases serum brain-derived neurotrophic factor level and decreases inflammation in parkinson's disease patients. *Journal of Physiology and Pharmacology*, *65*(3), 441-448. https://pubmed.ncbi.nlm.nih.gov/24930517/

Zuardi, A. W., Crippa, J. A., Hallak, J. E., Pinto, J. P., Chagas, M. H., Rodrigues, G. G., Dursun, S. M., & Tumas, V. (2009). Cannabidiol for the treatment of psychosis in parkinson's disease. *Journal of Psychopharmacology*, *23*(8), 979-983. https://doi.org/10.1177/0269881108096519

Zupan, M. F., Arata, A. W., Dawson, L. H., Wile, A. L., Payn, T. L., & Hannon, M. E. (2009). Wingate anaerobic test peak power and anaerobic capacity classifications for men and women intercollegiate athletes. *Journal of Strength and Conditioning Research*, *23*(9), 2598-2604. https://doi.org/10.1519/JSC.0b013e3181b1b21b

APPENDIX A

INSTITUTIONAL REVIEW BOARD APPROVAL

UNIVERSITY OF
NORTHERN COLORADO

Institutional Review Board

Date:	07/29/2020
Principal Investigator:	Laura Stewart
Committee Action:	**Expedited Approval - New Protocol**
Action Date:	06/19/2020
Protocol Number:	2005001624
Protocol Title:	CBD, Inflammation, & Natural Killer Cell Study (CINS)
Expiration Date:	

The University of Northern Colorado Institutional Review Board has granted approval for the above referenced protocol. Your protocol was approved under expedited category (2) as outlined below:

Category 2: Collection of blood samples by finger stick, heel stick, ear stick, or venipuncture as follows: (a) from healthy, nonpregnant adults who weigh at least 110 pounds. For these subjects, the amounts drawn may not exceed 550 ml in an 8 week period and collection may not occur more frequently than 2 times per week; or (b) from other adults and children2, considering the age, weight, and health of the subjects, the collection procedure, the amount of blood to be collected, and the frequency with which it will be collected. For these subjects, the amount drawn may not exceed the lesser of 50 ml or 3 ml per kg in an 8 week period and collection may not occur more frequently than 2 times per week.

All research must be conducted in accordance with the procedures outlined in your approved protocol.

If continuing review is required for your research, your project is approved until the expiration date listed above. The investigator will need to submit a request for Continuing Review at least 30 days prior to the expiration date. If the study's approval expires, investigators must stop all research activities immediately (including data analysis) and contact the Office of Research and Sponsored Programs for guidance.

If your study has not been assigned an expiration date, continuing review is not required for your research.

For the duration of the research, the investigator(s) must:

UNIVERSITY OF
NORTHERN COLORADO

Institutional Review Board

- Submit any change in the research design, investigators, and any new or revised study documents (including consent forms, questionnaires, advertisements, etc.) to the UNC IRB and receive approval before implementing the changes.
- Use only a copy of the UNC IRB approved consent and/or assent forms. The investigator bears the responsibility for obtaining informed consent from all subjects prior to the start of the study procedures.
- Inform the UNC IRB immediately of an Unanticipated Problems involving risks to subjects or others and serious and unexpected adverse events.
- Report all Non-Compliance issues or complaints regarding the project promptly to the UNC IRB.

As principal investigator of this research project, you are responsible to:

- Conduct the research in a manner consistent with the requirements of the IRB and federal regulations 45 CFR 46.
- Obtain informed consent and research privacy authorizations using the currently approved forms and retain all original, signed forms, if applicable.
- Request approval from the IRB prior to implementing any/all modifications.
- Promptly report to the IRB any unanticipated problems involving risks to subjects or others and serious and unexpected adverse events.
- Maintain accurate and complete study records.
- Report all Non-Compliance issues or complaints regarding the project promptly to the IRB.

Please note that all research records must be retained for a minimum of three (3) years after the conclusion of the project. Once your project is complete, please submit the Closing Report Form.

If you have any questions, please contact Nicole Morse, Research Compliance Manager, at 970-351-1910 or nicole.morse@unco.edu. Please include your Protocol Number in all future correspondence. Best of luck with your research!

Sincerely,

Mark Montemayor
Chair, Institutional Review Board

Carter Hall 3002 | Campus Box 143 | Greeley, CO 80639 | Office 970-351-1910 | Fax 970-351-1934

APPENDIX B

CERTIFICATE OF ANALYSIS

PROVERDE LABORATORIES

Test Certificate

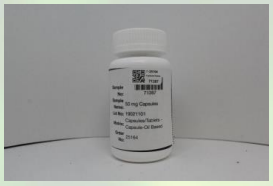
Certificate ID: **71387**
Client Sample ID: **50 mg Capsules**
Lot Number: **19021101**
Matrix: **Capsules/Tablets - Capsule-Oil Based**

Received: **11/22/19**

Scan QR Code for authenticity

6° Wellness
1002 Walnut St., Suite 300
Boulder, CO 80302
Attn: Jonny Lisano

Authorization:	Signature:	Date:
Elizabeth R. Wagoner, Lab Director		12/2/2019



PJLA Testing
Accreditation
80585

The data contained within this report was collected in accordance with the requirements of ISO/IEC17025:2017. I attest that the information contained within the report has been reviewed for accuracy and checked against the quality control requirements for each method. These results relate only to the test article listed in this report. Reports may not be reproduced except in their entirety.

CN: Cannabinoid Profile & Potency [WI-10-17 & WI-10-17-01]

Analyst: JSG *Test Date: 11/27/2019*

The client sample was analyzed for plant-based cannabinoids by Liquid Chromatography (LC). The collected data was compared to data collected for certified reference standards at known concentrations.

71387-CN

ID	Weight %	Concentration (mg/Capsule)
D9-THC	ND	ND
THCV	ND	ND
CBD	11.55	52.71
CBDV	0.03	0.14
CBG	ND	ND
CBC	ND	ND
CBN	ND	ND
THCA	ND	ND
CBDA	ND	ND
CBGA	ND	ND
D8-THC	ND	ND
exo-THC	ND	ND
Total	11.58	52.85
Max THC	ND	ND
Max CBD	11.55	52.71

0% Cannabinoids (wt%) 11.6%

Limit of Quantitation (LOQ) = 0.009 wt%

Max THC (and Max CBD) are calculated values for total cannabinoids after heating, assuming complete decarboxylation of the acid to the neutral form. It is calculated based on the weight loss of the acid group during decarboxylation: Max THC = (0.877 x THCA) + THC. This calculation does not include other cannabinoid isomers (eg. D8-THC and exo-THC). ND = None detected above the limits of detection (LOD), which is half of LOQ.

HM: Heavy Metal Analysis [WI-10-13]

Analyst: CJS Test Date: 11/25/2019

This test method was performed in accordance with the requirements of ISO/IEC 17025. These results relate only to the test article listed in this report. Reports may not be reproduced except in their entirety.

71387-HM

Symbol	Metal	Conc. [1] (µg/kg)	RL	Use Limits [2] (µg/kg) All	Use Limits [2] (µg/kg) Ingestion	Status
As	Arsenic	ND	50	200	1500	PASS
Cd	Cadmium	ND	50	200	500	PASS
Hg	Mercury	ND	50	100	1500	PASS
Pb	Lead	ND	50	500	1000	PASS

1) ND = None detected to Lowest Limits of Detection (LLD)
2) MA Dept. of Public Health: Protocol for MMJ and MIPS, Exhibit 4(a) for all products.
3)USP exposure limits based on daily oral dosing of 1g of concentrate for a 110 lb person.

MB1: Microbiological Contaminants [WI-10-09]

Analyst: AEG Test Date: 11/26/2019

This test method was performed in accordance with the requirements of ISO/IEC 17025. These results relate only to the test article listed in this report. Reports may not be reproduced except in their entirety.

71387-MB1

Symbol	Analysis	Results	Units	Limits*	Status
AC	Total Aerobic Bacterial Count	<100	CFU/g	100,000 CFU/g	PASS
CC	Total Coliform Bacterial Count	<100	CFU/g	1,000 CFU/g	PASS
EB	Total Bile Tolerant Gram Negative Count	<100	CFU/g	1,000 CFU/g	PASS
YM	Total Yeast & Mold	<100	CFU/g	10,000 CFU/g	PASS

Note: All recorded Microbiological tests are within the established limits.

MB2: Pathogenic Bacterial Contaminants [WI-10-10]

Analyst: LabAdmin Test Date: 11/27/2019

This test method was performed in accordance with the requirements of ISO/IEC 17025. These results relate only to the test article listed in this report. Reports may not be reproduced except in their entirety.

71387-MB2

Test ID	Analysis	Results	Units	Limits*	Status
71387-ECPT	E. coli (O157)	Negative	NA	Non Detected	PASS
71387-SPT	Salmonella	Negative	NA	Non Detected	PASS

Note: All recorded pathogenic bacteria tests passed.