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A Cross Sectional Comparison of the Mental Health, Sleep, and Anaerobic Power of Cannabis Users, Cannabidiol Users, and Non Users

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A CROSS SECTIONAL COMPARISON OF THE MENTAL HEALTH, SLEEP, AND ANAEROBIC POWER OF CANNABIS USERS, CANNABIDIOL USERS, AND NON USERS

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ABSTRACT

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Purpose: The purpose of this study was to determine whether there are differences among groups of individuals who regularly use cannabis, cannabidiol (CBD), or who are non-users with respect to mental health, sleep, and anaerobic power measures. **Methods:** A total of 24 participants (21 males and 3 females) were recruited and placed into groups based on their regular cannabis/CBD or non-cannabis/CBD use. The cannabis user group was using cannabis at least three times per week for the past 8 weeks (CA; n=8), the CBD user group was using CBD at least three times per week for the past 8 weeks (CB; n=8), and the control group was not using any cannabis or CBD product within the past 8 weeks (CO; n=8). Participants completed 2 total visits. During these visits, they completed a body composition evaluation using air displacement plethysmography with a BODPOD (COSMED USA Inc., Concord, CA), a physical activity assessment using the Physical Activity Readiness Questionnaire (PARQ) and International Physical Activity Questionnaire (IPAQ), mental health evaluation using the Psychological Wellbeing Scale (PWB), Generalized Anxiety Disorder-7 (GAD-7), Piper Fatigue Scale (PFS), and Ferrans and Powers Quality of Life Index (QOL) surveys, a subjective sleep quality survey using the Leeds Sleep Evaluation Questionnaire (LSEQ), and an anaerobic fitness assessment using the Wingate anaerobic power test on a cycle ergometer (Monark Ergomedic 894E, Monark, Varberg, Sweden). Additionally, the participants in the CA group completed a Daily

Sessions, Frequency, Age of Onset, and Quantity of Cannabis Use Inventory (DFAQ-CU) to measure cannabis use. **Results:** Mean PWB scores of CB and CO were significantly higher in the Autonomy ($p<0.001$; $p=0.003$), Personal Growth ($p<0.001$; $p<0.001$), Positive Relations with Others ($p=0.001$; $p=0.002$), Purpose in Life ($p=0.003$; $p=0.003$), and Self-Acceptance ($p=0.001$; $p=0.02$) subscales, respectively, when compared to CA. There were no significant differences in mean PWB scores between CB and CO in all PWB subscales ($p>0.05$). Mean QOL score of CB was significantly higher than the mean score of CA ($p=0.004$), but no significant differences were found between CA and CO ($p=0.11$) or CB and CO ($p=0.48$). Mean GAD-7 ($p=0.40$) and PFS ($p=0.25$) scores were not significant between groups. Mean LSEQ ($p=0.42$), GTS ($p=0.44$), QOS ($p=0.29$), AFS ($p=0.14$), and BFW ($p=0.14$) scores were not significant between groups. There were no significant differences between the groups in terms of average peak power ($p=0.77$), relative peak power ($p=0.15$), mean power ($p=0.97$), relative mean power ($p=0.30$), and anaerobic fatigue ($p=0.82$) during the Wingate assessment. **Conclusion:** The present study demonstrated no significant differences between CA, CB, and CO with respect to measures of anxiety, subjective fatigue, perceived sleep quality, and anaerobic power, but revealed significant differences between CA and both CB and CO in measures of psychological wellbeing and quality of life. These results suggest that regular cannabis users may have a lower psychological state and a lower perceived quality of life when compared to CBD users or cannabis and CBD non-users. Findings from this study provide a novel insight into the mental health, subjective sleep, and anaerobic power measures of regular cannabis users, regular CBD users, and a group of non-users.

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CHAPTER I

INTRODUCTION

Background

Cannabis, or more commonly referred to as marijuana, is one of the most frequently used recreational and federally illegal drugs in the United States with about 17.9% of Americans, or 49.6 million people, using or consuming the plant at least once in 2020 (Substance Abuse and Mental Health Services Administration, 2021). The legalization of cannabis for recreational use across many states has also substantially increased accessibility to the general population. In addition, the perception of the risks of cannabis has decreased in the United States since its legalization by an increasing number of individual states. Furthermore, the National Survey on Drug Use and Health conducted from 2002-2014 found that people aged ≥18 years old reported increased overall use of cannabis and a decreased perception of the risks of cannabis (Azofeifa et al., 2016).

Cannabis is derived from the *Cannabis* genus of plants and is composed of many genus-specific molecules, with delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD) emerging as two of the most widely studied compounds (Amin & Ali, 2019). The compound THC is regarded as the main psychoactive component of cannabis, while CBD is recognized as the non-psychoactive ingredient (Amin & Ali, 2019). Although these compounds may provide different effects on the body and research exploring the health effects of these compounds is ongoing, THC and CBD are both utilized as naturopathic and therapeutic remedies for physiological and

psychological complications. In the medical field, THC is used to treat chronic neuropathic pain (Lynch & Campbell, 2011), while the prescription forms of THC, dronabinol (Marinol®) and nabilone (Cesamet®), are both used to treat chemotherapy-induced nausea and vomiting (Todaro, 2012). The prescription form of CBD, Epidiolex®, is approved for use in patients afflicted with two rare forms of epilepsy, Lennox-Gastaut syndrome and Dravet syndrome (Abu-Sawwa et al., 2020). Along with therapeutic interventions for certain diseases or conditions, THC and CBD are also used naturopathically as home remedies. However, further insight into their side-effects and complications is needed before their use is considered innocuous.

Fatigue is a common symptom of many physiological and neurological conditions and is one of the most frequently reported symptoms by patients in primary care (Abd-Elfattah et al., 2015; Stadje et al., 2016). In addition, fatigue is associated with not only a lack of sleep or poor sleep quality (Moul et al., 2002), but also with depression and anxiety (Grandner et al., 2021). These findings suggest that fatigue is multifactorial and can be caused by both physiological and psychological complications. Due to the prevalence of fatigue in patients suffering from mental health and sleep complications, insights into a novel treatment of cannabis and cannabinoids may prove beneficial in the development of non-pharmaceutical, naturopathic interventions.

Previous literature provides support for the use of cannabis as an alleviating treatment for fatigue as well as the symptoms associated with the development of fatigue (Li et al., 2022). One study of 1,224 cannabis users reports that 91.94% of subjects experienced decreased fatigue following ingestion of cannabis flower (Li et al., 2022). Conversely, a systematic review of medical cannabis found that regular cannabis use is associated with greater risks of fatigue when compared to a placebo (AminiLari et al., 2022). Additionally, fatigue is one of the most reported side effects of cannabis use (Shannon et al., 2019).

Mental health complications, such as anxiety or depression, are also correlated to increased fatigue. Although CBD is believed to possess anxiolytic properties (Zuardi et al., 2017), cannabis and THC are also effective in improving anxiety and overall mental health (Blessing et al., 2015; Saugy et al., 2006). However, some studies contradict these findings as acute cannabis and THC use can be associated with increased anxiety (Fusar-Poli et al., 2009). Additionally, poor sleep quality is also associated with increased feelings of fatigue, but current literature on cannabinoids has led to mixed results on improving sleep quality (Babson & Bonn-Miller, 2014). In the literature, cannabis, THC, and CBD produce varied and opposing effects on subjective sleep quality and sleep measures with some studies reporting improvements to sleep measures (Bedi et al., 2010; Cousens & DiMascio, 1973; Shannon et al., 2019), while others are reporting decrements (Barratt et al., 1974; Kaul et al., 2021; Nicholson et al., 2004). The convoluted and opposing nature of cannabis and cannabinoids on sleep mechanisms and pathways is likely due to the significant role the endocannabinoid system plays in the regulation of the circadian sleep-wake cycle and the maintenance and promotion of sleep (Sanford et al., 2008; Vaughn et al., 2010).

Finally, anaerobic power is a measure of fatigability in skeletal muscles and current research on the effects of cannabinoids on this parameter is ongoing. One study from our lab revealed no differences in anaerobic measures between cannabis smokers and non-smokers (Lisano et al., 2019), while another study found that female cannabis smokers had less power generation in the first two stages of the Wingate protocol, but significantly less anaerobic fatigue when compared to non-smokers (Lisano et al., 2023). The relationship between cannabis and cannabinoids on mental health, sleep, and anaerobic power is unclear due to these confounding findings in the literature.

Although cannabis is mainly studied in clinical populations with a wide variety of chronic diseases, research on cannabis in healthy populations is scarce. Exploring the health-related effects of cannabis in a health population is especially important in society today due to the wide availability of cannabinoid products accessible to the general population and the intense cannabis company marking efforts aimed at healthy people. Therefore, further investigation exploring the relationship of THC and CBD as a treatment to improve mental health, sleep, and anaerobic power in healthy populations is warranted.

Statement of Problem

There is confounding literature exploring the relationship between THC and CBD on mental health, sleep, and anaerobic power in healthy populations. Cannabinoids, such as THC and CBD, have been used as a prescriptive medication to regulate chronic pain, but the association between cannabinoid use on mental health, sleep, and anaerobic power in a human model has yet to be explored comprehensively.

Rationale for Study

This study will be useful for individuals interested in the possible effects of cannabinoids as a novel intervention for improving mental health, sleep, and anaerobic power in healthy populations.

Purpose for Study

The purpose of this study was to determine whether there are differences among groups of individuals who regularly use cannabis, cannabidiol (CBD), or who are non-users with respect to mental health, sleep, and anaerobic power measures.

Research Hypothesis

H1 Cannabis and CBD users will have higher assessments of mental health and sleep and lower anaerobic power capability when compared to non-users.

CHAPTER II

REVIEW OF LITERATURE

Introduction

Cannabis use has become increasingly accepted with the legalization and availability of cannabis products (Azofeifa et al., 2016). The cannabinoids THC and CBD have received the most attention as possible therapeutic interventions for chronic diseases. However, the use of cannabinoids as a preventative or therapeutic interventions to improve mental health, sleep quality, and anaerobic power generation in healthy adults has yet to be explored comprehensively.

In this chapter, an overview of cannabis and cannabinoids, endocannabinoid system, mental health and fatigue, cannabinoids and mental health/fatigue, sleep, cannabinoids and sleep, anaerobic power, and cannabinoids and anaerobic power will be explored.

Cannabis and Cannabinoids

Cannabis is composed of at least 60 different compounds classified as cannabinoids, with the most widely studied cannabinoids being delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD) (Atakan, 2012). The earliest mentions of cannabis use dates to records from before the Common Era in China, Greece, Egypt, and the Roman Empire (Crocq, 2020). In ancient times, the use of cannabis was mainly used to treat mental disorders such as depression, but cannabis was also used as a topical treatment for inflammation as well (Crocq, 2020). These historical records suggest that the effects of cannabis were known to these ancient civilizations. Cannabis

use in Western medicine was widely accepted in Europe in the late 19th and early 20th century and its application was continued throughout the 1900s (Crocq, 2020). These western civilizations commonly used cannabis as an appetite stimulator as well as a sedative and analgesic prior to the discovery of other medications, such as aspirin (Crocq, 2020). Despite these potentially beneficial applications, in 1970, the United States categorized cannabis as a Schedule I substance with the passage of the Controlled Substances Act (CSA), thus restricting its use in the US and confounding further cannabis-related research (Crocq, 2020). However, since the legalization of recreational cannabis use in Colorado and Washington in 2012, recreational cannabis use is now legal in 19 different states as well as Washington, D.C. and Guam (Crocq, 2020). Additionally, the recent passing of the Farm Bill in 2018 has also led to the increased use of hemp in agriculture and textile production (Mead, 2019). The Farm Bill defined hemp as any component of the *Cannabis* plant, including its extracts and cannabinoids, that has a THC concentration of less than 0.3% (Mead, 2019). The Farm Bill was especially significant as it removed hemp as a Schedule I substance in the CSA, which has enabled CBD products that contain less than 0.3% to be available to the general public (Mead, 2019). With the increased availability of CBD products nationally from the Farm Bill and state legalization of THC, there has been a resurgence in cannabinoid research in recent years.

Cannabinoids are prenylated polyketides and are naturally produced in plants of the *Cannabis* genus (Tahir et al., 2021). Although cannabis is composed of over 400 chemical entities which includes over 60 different cannabinoids, the most abundant and researched of the cannabinoids are delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD) (Atakan, 2012). However, THC and CBD are not found in large concentrations in the *Cannabis* plants and are instead secondary products from their precursor's delta-9-tetrahydrocannabinolic acid A (THCA-

A) and cannabidiolic acid (CBDA), respectively (M. Wang et al., 2016). Both THCA-A and CBDA undergo decarboxylation with heat which then produces the secondary products THC and CBD needed for further interaction with the body's endocannabinoid system (ECS) (M. Wang et al., 2016). Although THC and CBD are structurally similar, they produce varying effects on the body. The cannabinoid THC is regarded as the main psychoactive component of cannabis, while CBD is recognized as the non-psychoactive ingredient (Amin & Ali, 2019).

Endocannabinoid System

The endocannabinoid system (ECS) is an important neuromodulatory system in the human body and plays a significant role in the function and regulation of the central nervous system (CNS), as well as skeletal muscle, immune, and endocrine tissue (Lanz et al., 2018). The body naturally produces endocannabinoids, including anandamide (AEA) and 2-arachidonoyl glycerol (2-AG) which play a regulatory role in maintaining homeostasis of immune, metabolic, vascular, and neuronal functions (Lanz et al., 2018; VanDolah et al., 2019). The ECS is composed of cannabinoid receptors (CB), endocannabinoids, and the enzymes required for their biosynthesis and degradation (Salzet, 2000).

Endocannabinoid receptors bind both exogenous cannabinoids and endocannabinoid compounds and act through cannabinoid 1 (CB1) and cannabinoid 2 (CB2) receptors (Alger, 2013). CB1 is the predominant cannabinoid receptor in the CNS, while CB2 is mainly found in the periphery (Alger, 2013). Both CB1 and CB2 are classified as G-protein coupled receptors and become activated through the inhibition of adenylate-cyclase when bound by their ligand (Alger, 2013; Oberbarnscheidt & Miller, 2017). In vivo, AEA and 2-AG are the primary endocannabinoid ligands for CB1 and CB2, respectively (Reggio, 2010). The CB1 receptor is the most abundant G-protein coupled receptor in the brain and found in regions associated with

cognition, memory, pain, anxiety, perception and motor function (Alger, 2013; Herkenham et al., 1990). Along with CB1, the CB2 receptor is also found in the CNS, but in lower concentrations (Joshi & Onaivi, 2019). Specifically, the CB2 receptor is mainly located in the periphery and is expressed on immune cells, such as T cells and macrophages, and hematopoietic cells (Joshi & Onaivi, 2019).

Tetrahydrocannabinol and Cannabidiol Actions in the Body

The metabolism of THC and CBD is dependent on how it enters the system. The most frequent routes of administration of THC and CBD are through inhalation, oral ingestion, oral mucosal/sublingual, rectal, and transcutaneous routes (Oberbarnscheidt & Miller, 2017). When cannabis products are inhaled following decarboxylation, THC and CBD enters the lungs where it then passes into the bloodstream and rapidly binds to cannabinoid receptors (Chayasirisobhon, 2021; Oberbarnscheidt & Miller, 2017). When compared to inhalation, oral ingestion of THC and CBD results in a delayed response as it needs to metabolize in the gastrointestinal system before it can pass into the bloodstream (Huestis, 2007). Additionally, first pass metabolism occurs when cannabinoids are ingested or absorbed through the digestive tract which results in only a fraction of cannabinoids being available in the bloodstream (Lamarine, 2012). When cannabinoids are ingested sublingually, they are rapidly absorbed by the oral mucosa into the bloodstream which results in a much quicker response when compared to oral ingestion (Lucas et al., 2018). Rectal administration of natural and synthetic cannabinoids using suppositories is quickly absorbed into the bloodstream through the lining of the intestinal wall (Huestis, 2007). Transcutaneous administration of cannabinoids is much slower when compared to the other administration routes as transport and absorption across the skin is limited by the hydrophobic

qualities of cannabis (Lamarine, 2012). Regardless of the route of administration, once these cannabinoids circulate throughout the body and bind or interact with their endocannabinoid receptors, this causes the physiological and psychological changes seen in the brain or in the body.

The compounds THC and CBD bind to and affect the endocannabinoid systems in different ways. THC is a partial agonist to both CB1 (Ki = 40.7 nM) and CB2 (Ki = 36 nM) receptors (Bow & Rimoldi, 2016). When THC is bound to CB1, this interaction results in the downregulation of the cAMP signaling pathways by inhibiting adenylate cyclase, which in turn causes the observed psychotropic effects of euphoria and relaxation (Hua et al., 2016). Conversely, CBD has a low binding affinity to the endocannabinoid receptors and instead functions as an antagonist in the presence of THC (Thomas et al., 2007). In fact, CBD functions as a CB1 antagonist, a non-competitive allosteric modulator of CB2, and indirectly diminishes the efficacy of THC (Laprairie et al., 2015).

Health Effects of Tetrahydrocannabinol and Cannabidiol

In terms of pulmonary function, THC inhalation has varying results. In one study, the researchers found that THC use is associated with a higher total lung capacity and forced vital capacity (FVC) (Hancox et al., 2010). Conversely, in another study, THC inhalation was associated with a dose-related impairment of airway function that resulted in hyperinflation and airflow obstruction (Aldington et al., 2007). In addition, previous literature has found that acute administration of inhaled THC resulted in bronchodilation within asthmatic patients (Hartley et al., 1978; Williams et al., 1976). In comparison to tobacco, cannabis inhalation caused similar symptoms when compared to tobacco inhalation, such as chronic bronchitis and large airway

pathological changes (L. Ribeiro & Ind, 2016). However, unlike tobacco, the mechanisms by which cannabis affects the pulmonary system is still unclear in the literature.

Conversely, CBD improves pulmonary function in animal models. In one study, a five times diluted CBD-containing compound NCMB-1 was found to improve tidal volume, inspiratory flow rate, and respiration rate in the fibrotic lungs of African Green Monkeys when compared to a control (Webb et al., 2020). Additionally, CBD administration decreased total lung resistance and elastance in mice subjected to acute lipopolysaccharide (LPS)-induced lung injury (A. Ribeiro et al., 2015).

Both THC and CBD are also associated with physiological changes in cardiovascular function. One study found that acute administration of THC increases resting heart rate (HR) by 30-50% in human subjects (Hart et al., 2005). Similarly, these results were replicated in another investigation, which concluded that THC use resulted in an acute, dose-dependent increase in both HR and blood pressure (BP) (Mittleman et al., 2001). Interestingly, this same study also concluded that the risk of myocardial infarction onset was 4.8 times greater than baseline in the first 60 minutes after initial use of cannabis, but this elevated risk rapidly decreased thereafter (Mittleman et al., 2001). Furthermore, chronic THC or cannabis use has also been associated with increased angina frequency (Jones, 2002) as well transient ischemic attack (Mouzak et al., 2000).

In terms of CBD, a meta-analysis concluded that CBD (100-1200mg) administration in humans had no effect on resting HR (Sultan et al., 2017). But in that same meta-analysis, CBD administration attenuated “stress-induced” increases in HR and BP (Sultan et al., 2017). The results of these studies suggest that THC is the main component that causes the observed cardiovascular changes, while CBD alone is not as impactful. However, further investigation is

warranted in order to determine whether the combination of CBD and THC could exacerbate or attenuate these cardiovascular changes.

Tetrahydrocannabinol, Cannabidiol, and Pain

Pain and pain relief is one of the most commonly cited reasons for medicinal use of cannabis (Vučković et al., 2018). Medically, THC has been shown in the literature to be moderately effective and a safe treatment option for chronic neuropathic pain (Lynch & Campbell, 2011). One longitudinal study of 751 chronic pain patients undergoing individualized medicinal THC treatment over a 12-month period found that THC use was associated with improvements to pain severity and interference (Safakish et al., 2020). Additionally, multiple preclinical studies using an oral mucosal spray of cannabis extract (Sativex®), a compound containing a 1:1 ratio of THC to CBD, have yielded promising initial results in treating chronic neuropathic pain (Hoggart et al., 2015; Lichtman et al., 2018; Russo et al., 2016).

Similarly, CBD alone has also been studied in mice for the treatment of neuropathic pain with positive analgesic effects (Casey et al., 2017; Harris et al., 2016), albeit with less effectiveness than THC or gabapentin alone (Harris et al., 2016). However, similar to all analgesics, the pain alleviating effects of cannabinoid treatment are not effective across all types of chronic pain and are dependent on the dosage, person, and type of pain being experienced (Vučković et al., 2018). In human models, a recent study of 400 chronic pain patients found that daily oral intake of 100mg of CBD oil resulted in self-reported improvements to pain and quality of life (Gulbransen et al., 2020). Although current research shows promising results, further investigation into the physiological mechanisms and therapeutic dosages is needed before prescription of cannabinoids for pain can be issued safely.

Mental Health and Fatigue

Mental health disorders are a major public health challenge in the United States with 21% of adults 18 years or older (59.2 million) experiencing mental illness in the past year (Substance Abuse and Mental Health Services Administration, 2021). Anxiety and depression are two of the most common mental health concerns in our society and tend to go undiagnosed and untreated (Trudgen & Lawn, 2011). Anxiety and depression are highly comorbid, with anxiety presenting prior to the development of depression (Kalin, 2021). Furthermore, about 85% of patients with depression disorders also have anxiety, and comorbid depression has been shown to occur in up to 90% of patients with anxiety disorders (Gorman, 1996). Additionally, the presence of anxiety and depression can be debilitating and the combination of the two disorders have been linked to an increased risk for suicidal ideation and behavior (Cougle et al., 2009; Perroud et al., 2007).

Anxiety disorders are the most prevalent psychiatric disorders with about 29% of the population in the United States suffering from at least one anxiety disorder (Kessler et al., 2005). Anxiety can be defined as a prolonged state of apprehension caused by an unpredictable or undisclosed possible threat or danger (Knight & Depue, 2019). Individuals afflicted with anxiety disorders report lower levels of life satisfaction and well-being, as well as higher levels of impairment in overall functioning (Wittchen et al., 2000). The development of anxiety is multifaceted and could be caused by multiple physiological, psychological, and environmental risk factors. Psychological risk factors that play a role in the development of anxiety include neuroticism, perfectionism, and intolerance of uncertainty (Barlow, 2004), while social and familial risk factors include childhood physical and sexual abuse or neglect, family history of anxiety, early separation from families, and acute and chronic stress (Breslau et al., 1999). Although anxiety can be stabilized medically with medications and naturally with meditation and

mindfulness training, further investigation should be warranted due to its high prevalence rate in society.

Depression is a mental health disorder characterized by chronic feelings of sadness, emptiness, or irritability, accompanied with changes in an individual's ability to function normally (American Psychiatric Association, 2022). Depression and depressive disorders are a global mental health crisis with a lifetime prevalence of 20%-25% in women and 7%-12% in men (World Health Organization, 2002). Furthermore, patients experiencing depression have a higher risk in engaging in suicidal behaviors (Hawton et al., 2013), which is further corroborated by the fact that 50% of suicide victims meet the diagnostic criteria for a depressive disorder (Joiner et al., 2005; McGirr et al., 2007). A few of the various risk factors for depression include substance abuse (Coelho et al., 2000), childhood trauma (Martins-Monteverde et al., 2019), and family history of depression (Hodgson & McGuffin, 2012). Depression is a debilitating condition and because it has been linked to suicidal ideations and suicide success, it is an important psychiatric condition to screen for and treat at the first sign of symptoms. Extensive research on the pathology of mental health disorders and its symptoms has been reported elsewhere and is beyond the scope of this review.

Fatigue is commonly found in patients exhibiting psychiatric disorders and is a diagnostic criterion needed to diagnose both anxiety and depression (American Psychiatric Association, 2022). Fatigue is therefore an important determinant in the diagnosis of mental health disorders and a debilitating symptom caused by those same disorders. The current pathophysiology of fatigue suggests that the presentation of fatigue is mediated by central and peripheral mechanisms of the body (Jason, et al., 2010). Central fatigue is caused by changes in neurotransmitter concentrations in the brain, resulting in a deficient drive in motor cortical output

(Tornero-Aguilera et al., 2022). Peripheral fatigue is the decrease in the contractile muscle strength that results from changes in the mechanisms underlying the transmission of action potentials during a voluntary movement (Zając et al., 2015).

In the context of mental health, the central fatigue mechanism is of greater importance. Within the central fatigue theory, concentrations of neurotransmitters play an important role in the regulation and onset of fatigue. Of primary importance are the monoamines serotonin, dopamine, and noradrenaline, where changes in the concentrations of these neurotransmitters are associated with changes in motivation, mood, and fatigue onset (Tornero-Aguilera et al., 2022). These findings are further corroborated with the monoamine hypothesis of depression which suggests that deficiencies or imbalances of these monoamines are the cause of depression (Lee et al., 2010). This initial hypothesis was further supported by early iterations of anti-depressants which acutely enhanced monoamine function (Ressler & Nemeroff, 2000). Additionally, the use of selective serotonin reuptake inhibitors (SSRIs) as an effective anti-depressant treatment also provided support for this early hypothesis (Renard et al., 2001). Current literature supports the notion of fatigue and mental health as being multifaceted and caused by many different physiological, psychological, and environmental factors, but the relationship between central fatigue and mood disorders should still be emphasized.

Cannabinoids and Mental Health/Fatigue

Tetrahydrocannabinol, Cannabidiol, and Anxiety

Cannabinoids, especially THC, has been established as a mood changer due to the euphoric effects following ingestion (Lucatch et al., 2018). However, acute cannabis and THC use is also associated with impaired learning, memory loss, decreased attention, and decreased

motor coordination (Hill et al., 2022). Additionally, cannabis intoxication is also associated with increased feelings of anxiety, paranoia, and psychosis (Hill et al., 2022). With the advent of legalization and the increased availability and potency of cannabis products, there are increased risks for adverse outcomes, including mental health (Page et al., 2020).

Chronic cannabis use has undergone substantial investigation in the realm of psychiatry as a possible cause of mental health disorders. In a systematic review, the researchers determined that patients with anxiety disorders also have relatively high rates of cannabis and THC use, but it is still unclear whether cannabis use is also associated with an increased risk of developing long-term anxiety disorders (Crippa et al., 2009). Additionally, this review also found that the anxiogenic effects of acute THC use were pronounced in infrequent or non-users when compared to frequent users (Crippa et al., 2009). This suggests that tolerance may play a role in the perceived anxiogenic effects of THC. Furthermore, another study found that intravenous administration of 2.5mg or 5mg of THC prior to a visual analog scale (VAS) for anxiety test found that both dosages resulted in higher anxiety scores on the VAS test when compared to a placebo group (D'Souza et al., 2004). These results were further corroborated an additional study which found that oral ingestion of 0.5mg/kg or 10mg of THC resulted in increased anxiety as noted on a State-Trait Anxiety Inventory (STAI) when compared to CBD or placebo groups (Fusar-Poli et al., 2009).

However, there are some studies that have linked cannabinoids to improvements in anxiety. Specifically, CBD exhibits anxiolytic properties. In mouse models, 50 mg/kg of chronic CBD injections administered intraperitoneally produced moderate anxiolytic effects in an open-field anxiety test, while 1 mg/kg of chronic intraperitoneal CBD injections produced similar anxiolytic effects during a light-dark anxiety test (Long et al., 2010). In human models, CBD

significantly decreases social anxiety and cognitive impairment during a public speaking test when compared to a healthy control or placebo (Bergamaschi et al., 2011; Zuardi et al., 1993). Additionally, daily oral ingestion of 25mg of CBD was found to significantly decrease subjective anxiety scores on the Hamilton Anxiety Rating Scale in 57 out of 72 adults in the first month of treatment for anxiety at a psychiatric outpatient clinic and remained decreased at the 3 month conclusion of treatment (Shannon et al., 2019). Based on the current literature, CBD and not THC is the main anxiolytic component of cannabis that could be linked to improvements in anxiety and overall mental health, but further investigation is warranted to further elucidate the psychophysiological changes that occur with regular cannabis use.

Tetrahydrocannabinol, Cannabidiol, and Depression

Current literature suggests that THC use and depression may have a significant correlation. A meta-analysis concluded that chronic or heavy THC is associated with an increased risk of developing depressive disorders (Lev-Ran et al., 2014). These results were further supported by another study which found that depression was positively and significantly associated with THC use (Dierker et al., 2018). Additionally, a recent survey analysis of 281,650 young adults aged 18–34 revealed that THC use was positively associated with increased risk of suicidal ideation, planning, and attempts (Han et al., 2021). However, two population-based longitudinal studies suggest that THC use, even chronic use, was not associated with an increased incidence of major depressive disorders, after controlling for baseline confounders (Danielsson et al., 2016; Feingold et al., 2015). The literature is currently undecided on whether THC use is associated with developing depression, thus further investigation is warranted.

In terms of CBD, there is some evidence to support the use of CBD in alleviating depressive symptoms. In mouse models, intravenous injection of 10mg/kg or oral administration of 100mg/kg of CBD in Institute of Cancer Research (ICR) mice resulted in antidepressant behavioral effects during a forced swim test (Xu et al., 2019). In human models, one study of twenty chronic cannabis users found that daily oral ingestion of 200mg of CBD resulted in decreased depressive and psychotic-like symptoms and improvements to attention, memory, and verbal learning when compared to baseline (Solowij et al., 2018). In addition, a survey study of 1483 subjects who use CBD daily revealed that 400 subjects used CBD for mood-improvement effects with positive results (Corroon & Phillips, 2018). However, this study did not differentiate between synthetic or natural CBD-products, thus the CBD-product used may have contained THC as well. Due to the availability of unregulated CBD-products, further investigation is warranted before CBD can be considered a safe and effective treatment for depression.

Tetrahydrocannabinol, Cannabidiol, and Fatigue

In previous literature, *Cannabis* flower has varying effects on fatigue. In a survey study of 538 people with Parkinson's disease and multiple sclerosis, cannabis users reported lower levels of fatigue compared to non-users (Kindred et al., 2017). Similarly, in a study of 751 chronic pain patients that underwent medical cannabis treatment, perceived fatigue improved as a result of cannabis use when compared to baseline (Safakish et al., 2020). One study of 1,224 Cannabis users reports that 91.94% of subjects experienced decreased fatigue following ingestion of *Cannabis* flower *in vivo* (Li et al., 2022). Conversely, a systematic review of medical cannabis found that regular cannabis use is associated with greater risks of fatigue when compared to a placebo (AminiLari et al., 2022). Additionally, fatigue is one of the most reported

side effects of cannabis use (Shannon et al., 2019). Although many studies evaluated perceived or self-reported fatigue, it can be inferred that cannabis use plays a role in the mechanisms of fatigue, whether it be inducing or alleviating.

In the current literature, there are very few studies investigating isolated THC and its effects of fatigue. In one study of 1,120 cancer patients, 300 subjects reported a 30% improvement to fatigue following 4 months of self-administered THC use (Anderson et al., 2019). However, there is evidence to support the association between THC and lack of motivation and laziness, possibly exacerbating the symptoms of chronic fatigue (Pacheco-Colón et al., 2018). Additionally, many studies have looked at the effects of *Cannabis* flower on fatigue and not isolated THC, which explains the current dearth of literature in the area. Further investigations are needed before isolated THC can be utilized as a treatment for fatigue.

In terms of CBD, there is some evidence to support the use of CBD as a treatment for subjective fatigue. In one study of 371 subjects with autoimmune hepatitis, 38% of patients reported using CBD for fatigue with 61% of respondents reporting significant improvements to subjective fatigue (Mathur et al., 2020). Conversely, another study found that 5mg/kg oral administration of CBD was not effective in improving subjective fatigue in physically active individuals when compared to a placebo (Crossland et al., 2022). Similar to studies investigating THC, current investigations into other cannabinoids have focused on improving subjective fatigue. Consequently, their results may be confounded with biases and underlying baseline complications. Since fatigue is multifactorial, further investigation into the effects of cannabis on the physiological and psychological mechanisms of fatigue is warranted.

Sleep

Sleep is an important physiological tool that plays a vital role in maintaining brain function and systemic physiological functioning (Medic et al., 2017). The lack of sleep or poor sleep quality has been linked to many chronic diseases such as chronic fatigue, diabetes, and heart disease (Gottlieb et al., 2005; Wolk et al., 2005), and mental health disorders such as anxiety and depression (Franzen & Buysse, 2008). It is recommended that adults aged 18-60 should sleep for 7 or more hours to promote optimal health, but it is estimated that one-third of United States' adults do not meet this recommendation (Watson et al., 2015).

Sleep disorders are also prevalent today in the United States, with obstructive sleep apnea (OSA), insomnia, and restless leg syndrome (RLS) being the most frequently diagnosed. Obstructive sleep apnea is characterized by the blockage of the upper airways during sleep which results in the sleeper not breathing for periods of time and it is estimated that 17% of women and 34% of men in the United States are afflicted with OSA (Gottlieb & Punjabi, 2020). Insomnia is a sleep disorder that results in an inability to sleep, and it is estimated that about 10%-13% of adults suffer from chronic insomnia (Roth, 2007). Restless leg syndrome is a neurologic disease and is characterized by an uncontrollable urge to move one's legs and it is estimated that 4%-29% of adults experience these sensations (Innes et al., 2011). The prevalence of sleep disorders contributes to the poor quality and lack of sleep seen in society.

In mammals, the sleep cycle can be divided into one stage of rapid eye movement (REM) sleep and four stages of non-rapid eye movement (NREM) sleep with stages 3 and 4 commonly known as slow wave sleep (Medic et al., 2017). In order to evaluate and quantify sleep and progression through the sleep cycle, researchers utilize many different techniques such as electroencephalogram (EEG), electromyography (EMG), electrooculography (EOG), and

polysomnography (PSG) (Carskadon & Dement, 2011; Marino et al., 2013). In modern sleep research, PSG is the gold standard for measuring sleep and utilizes EEG, EMG, and EOG techniques to record eye movement, muscle activity, and brain activity, respectively during a bout of sleep (Marino et al., 2013). During one series of the sleep cycle, a person begins in NREM sleep and progresses through its four stages and is immediately followed by REM sleep. These sleep cycles occur approximately 4 to 6 times per night with each cycle lasting about 90 minutes each (Memar & Faradji, 2018). Extensive investigation on the physiological mechanisms of the sleep cycle is reported elsewhere and are beyond the scope of this review.

Cannabinoids and Sleep

Early research on the effects of the cannabis plant as a sleep aid began in the 1970s with varying results. A few studies reported that the use of the cannabis flower had positive effects such as decreased sleep onset latency (Cousens & DiMascio, 1973) and wakefulness after sleep onset (Pivik et al., 1972), while others reported negative effects including decreased REM (Feinberg et al., 1976) and increased slow wave sleep (Barratt et al., 1974). In more recent years, the potential of cannabis to alter sleep was further supported when the endocannabinoid system was identified as a key player in the regulation of the circadian sleep-wake cycle and the maintenance and promotion of sleep (Sanford et al., 2008; Vaughn et al., 2010).

Both THC and CBD have varying effects on sleep measures. A recent clinical study involving dronabinol, a synthetic form of THC, in individuals with severe obstructive sleep apnea found that 2.5 mg and 10 mg doses of dronabinol taken daily for 42 and 28 days, respectively per FDA guidelines, correlated with significantly lower self-reported Epsworth Sleepiness Scale (ESS) scores when compared to baseline and a placebo control (Carley et al., 2018). Similarly, another study found that 10 mg of dronabinol ingested 4 times a day was

associated with increased subjective sleep quality and subjective decreases in sleep disturbances among HIV positive cannabis smokers during the first 8 days of a 16 day in-patient stay (Bedi et al., 2010).

In terms of CBD, one study using a mouse model found that CBD administration was shown to have sleep-inducing (20 mg/kg) and sleep-maintenance qualities (40mg/kg), but the effects were diminished due to tolerance after long-term administration (Monti, 1977). In human models, CBD also plays a role in the sleep-wake cycle and is dose dependent. Oral ingestion of 5 mg of CBD resulted in a decrease in stage 3 of slow wave sleep with further decreases in sleep quality and increased wakefulness at 15 mg of oral CBD (Nicholson et al., 2004). Conversely, oral ingestion of 160 mg of CBD was found to increase sleep duration in insomniac patients when compared to those receiving a placebo control (Carlini & Cunha, 1981). Although recent literature has assessed CBD as a potential treatment for sleep disorders, there is currently insufficient evidence to support its use as a therapeutic treatment at this time (Suraev et al., 2020).

Another important aspect to consider is the possibility of cannabis withdrawal as a component in poor sleep quality. Sleep disturbances and vivid dreams are considered the hallmark cannabis withdrawal symptoms and are particularly prevalent after chronic use of cannabis (Budney et al., 2003). These findings were similarly expressed in a cross-sectional study, which revealed that abrupt cessation of cannabis use among chronic users was correlated with a decrease in total sleep time, sleep efficiency, and %REM when measured with PSG (Bolla et al., 2010). This suggests that although cannabis use may have an acute benefit of inducing sleep and increasing tiredness, dependence and cessation of cannabis after regular use may attenuate these acute effects and result in a decreased quality and duration of sleep. Further

investigation into the effects of cannabinoids on sleep is warranted, especially in healthy and active populations and among chronic users.

Anaerobic Power

During a short duration, high intensity exercise, anaerobic metabolic systems such as the ATP-PCr and anaerobic glycolysis pathways are the main providers of the energy needed to sustain the activity (Baker et al., 2010). The goal of these anaerobic metabolic systems is the regeneration of ATP in order to sustain a maximal exertion activity or exercise in the absence of adequate oxygen consumption. During the first few seconds of maximal exercise, the stored ATP in the body is used to sustain muscle contraction and movement, but after these stores are depleted, the ATP-PCr system takes over to rapidly supply the required inorganic phosphate needed to regenerate ATP (Sahlin, 2014). After about 6 seconds of sustained maximal exercise, anaerobic glycolysis will dominate and supply the body with the required energy (Sahlin, 2014). The anaerobic glycolysis system functions by regenerating NAD^+ from NADH through the reduction of pyruvate to lactate by the lactate dehydrogenase enzyme, thus supplying glycolysis with the NAD^+ necessary to sustain the production of ATP from the breakdown of glucose (Driss & Vandewalle, 2013).

Anaerobic power and fatigue are most commonly assessed using the Wingate protocol with a cycle ergometer. The Wingate protocol evaluates the ability of the body's ATP-phosphocreatine (ATP-PCr) and anaerobic glycolysis systems by measuring the power generated during a maximal exertion cycle ergometer task and is representative of anaerobic power (Dekerle et al., 2008). The Wingate protocol measures anaerobic power and fatigue through three main indices: peak power output (PP), mean power output over the course of the test (MP), and the decrease in power (fatigue index) (Driss & Vandewalle, 2013). These three indices are

representative of the body's anaerobic capacity and fatigability during short-duration, high intensity exercises. The protocol of the Wingate test is composed of a warm-up on the cycle ergometer followed by 30 seconds of maximal effort pedaling against a constant resistance (7.5% of the subject's body weight) (Driss & Vandewalle, 2013). The optimal duration of the maximal exertion portion of the Wingate is highly debated in the literature. Previous studies have found that values obtained during 20 second durations for the maximal exertion phase are predictive of values obtained during the original 30 second durations (Attia et al., 2014; Stickley et al., 2008).

Cannabinoids and Anaerobic Power

There are few studies which explore the effects of THC or CBD on anaerobic power. Instead, many studies have explored anaerobic power in cannabis users and non-users. A study from our lab found that there were no significant differences between cannabis users and non-users with respect to anaerobic power such as peak power, minimum power, relative peak power, mean anaerobic power, and anaerobic capacity during a Wingate test in physically active males (Lisano et al., 2019). A more recent study with female cannabis users from our lab suggests that cannabis use results in less power generation in the first two stages of the Wingate assessment, but significantly less anaerobic fatigue when compared to non-users (Lisano et al., 2023). It is important to note that the frequency and method of cannabis use and the cannabinoid concentration of these products used by the cannabis users were not standardized between these two studies. Additionally, these studies instructed their subjects to abstain from cannabis for hours or days prior to testing, thus this may not represent the functional state for chronic users. In addition, these results may be confounded due to possible withdrawal effects as a result of chronic cannabis use and may not fully represent this population (Preuss et al., 2010). Thus,

additional insight into the effects of cannabinoids on anaerobic strength and power are needed in terms of chronic cannabis users before these findings are considered definitive.

Tetrahydrocannabinol, Cannabidiol, and Skeletal Muscle

Skeletal muscle structure and function is a major determinant of anaerobic power and fatigue. Previous studies confirmed the existence of endocannabinoid receptors within human skeletal muscle cells (Cavuoto et al., 2007), as well as within striated muscle mitochondria (Arrabal et al., 2015). This suggests that the endocannabinoid system plays a role within skeletal muscle and may affect energy generation and movement. In fact, recent developments in mice revealed that endocannabinoid signaling interferes with muscle metabolism (Lipina et al., 2016) and muscle maintenance (González-Mariscal et al., 2019). In human models, an acute bout of resistance exercise decreased CB1 expression on skeletal muscles cells of the *vastus lateralis* which resulted in increased skeletal muscle anabolic signaling processes in vitro (Pekkala et al., 2015). This suggests that CB1 receptor expression may cause an increase in muscle wasting and decrease in protein synthesis of skeletal muscles in human models. However, these developments are characterized to mice and human models in vitro and therefore may not be replicable with human models in vivo.

More recent studies have started to explore the effects of THC on skeletal muscle. One study found that acute THC administration (100 nM or 200 nM) added directly to the respiratory chambers of isolated striated skeletal muscles decreased mitochondrial oxidative respiration by 12-15% in wild-type C57BL/6N female mice (Mendizabal-Zubiaga et al., 2016). Additionally, THC administration also inhibited calcium (Ca^{2+}) release from the sarcoplasmic reticulum as well as a decrease in Ca^{2+} sensitivity resulting in enhanced muscle fatigability in mice (Oláh et

al., 2016). These findings suggest that THC administration may inhibit Ca^{2+} release by the sarcoplasmic reticulum, mitochondrial function, and the production of ATP, thereby resulting in decreased muscular functionality and increased muscular fatigue at lower workloads. However, these outcomes have yet to be fully explored.

A few studies have explored the muscle-related actions of CBD. One preclinical study found that administration of 10mg/kg of CBD injected intraperitoneally in doxorubicin treated myocardial tissues of male C57BL/6J mice improved mitochondrial activity and biogenesis (Hao et al., 2015). Similarly, another study concluded that acute (single dose) and chronic (once daily for 14 consecutive days) intraperitoneal injections of CBD (15, 30, or 60 mg/kg) in Wistar rats increased the activity of mitochondrial complexes and creatine kinase in rat brains (Valvassori et al., 2013). Another study found that 1-5 μM of CBD with insulin-like growth factor 1 (IGF-1) added to C2C12 myotubes *in vitro* showed no anabolic signaling through mTORC1, which suggests that CBD does not directly modulate anabolic or inflammatory pathways in cultured myotubes (Langer et al., 2022). Although these are preliminary studies, it is possible that CBD can both upregulate and inhibit mitochondrial activity and biogenesis in skeletal muscles; however, more research in human models is necessary.

CHAPTER III

METHODOLOGY

Healthy males and females (n=24) between the ages of 18-46 years of age were recruited from the University of Northern Colorado and the surrounding community to participate in this study. The cannabis user group was using cannabis at least three times per week for the past 8 weeks (CA; n=8), the CBD user group was using CBD at least three times per week for the past 8 weeks (CB; n=8), and the control group was not using any cannabis or CBD product within the past 8 weeks (CO; n=8). All participants were in good health and were training for at least 5 days a week for the past 3 months or 150 minutes of moderate to vigorous exercise per week for the past 3 months as defined by the guidelines set by the American College of Sports Medicine for an active individual (Liguori, 2021). Exclusion criteria included the presence of known chronic disease conditions, such as cardiovascular disease, cancer or diabetes, consistent use of anti-inflammatory medications or medications that act through the liver metabolism throughout the duration of this investigation, the presence of severe untreated anxiety or depression, have a BMI above 29.9 classifying them as obese, or any anticipated changes in their regular exercise regimen within the study intervention period.

Participants completed 2 total visits. During these visits, they completed a body composition analysis, anaerobic fitness analysis, physical activity, sleep quality, and mental health analyses. Each of the 2 visits took place in Gunther Hall Room 1610. All participants were able to safely complete all protocols described for the present study without any adverse events.

Visit 1

Informed Consent

Upon arrival at Gunter Hall Room 1610, all participants were instructed to complete an informed consent detailing the risks, benefits, and obligations of this study and were given time to review the document. The investigator explained the experimental protocol and answered any questions they may have. The subject and the researcher signed two copies of the informed consent (one for the subject to take; the other for the researcher's records) if the subject was willing to participate in the study. Following completion of the informed consent, the participant was then instructed to complete and turn in the questionnaires as listed below.

Medical Health History and Physical Activity Readiness Questionnaire (PAR-Q)

Participants completed a Medical History Form and a Physical Activity Readiness Questionnaire (PAR-Q), which are designed to elucidate the subject's past medical history and determine if the subject is safely able to perform any type of physical activity. These forms allowed the researcher to become aware of any potential health issues that might be exacerbated by physical activity. Both the Medical History Form and PAR-Q were completed and turned in during the first visit.

Physical Activity Questionnaire and Structured Exercise Questionnaire (IPAQ)

Participants completed the International Physical Activity Questionnaire (IPAQ), which provided information on physical activity and was completed in the week leading up to the present study (Craig et al., 2003). The IPAQ consists of 27 questions and includes sections regarding physical activity in the workplace, for transportation, in the home, for exercise or

leisure, as well as time spent sitting. The questionnaire was completed and turned in during the first visit and the participant was also instructed to answer a few questions about their regular exercise habits.

Body Weight and Height Assessment

Participants were instructed to remove their shoes, socks, and any additional clothing other than the participants base layer prior to height and weight assessment. Weight and height were obtained using a Detecto standing digital scale (Webb City, Missouri, USA) and the stadiometer SECA 220 (Chino, California, USA), respectively.

Air Displacement Plethysmography

Body composition, lean body mass (LBM) and body fat percentage (BF%) were evaluated using air displacement plethysmography using a calibrated BODPOD (COSMED USA Inc., Concord, CA). Participants were instructed to remove their shoes, socks, jewelry, and all additional clothing other than their base layer. Participants were then given a swim cap to wear and body composition analysis was performed per the manufacturer's guidelines (Tucker et al., 2014)

Marijuana Use Assessment (DFAQ-CU)

Participants in the cannabis use (CA) group were asked to complete the Daily Sessions, Frequency, Age of Onset, and Quantity of Cannabis Use Inventory (DFAQ-CU) (Cuttler & Spradlin, 2017). The DFAQ-CU is a 33-item questionnaire that includes items related to cannabis smoking rate, quantity, mode, and context of use, among other use patterns. The DFAQ-CU questionnaire was completed and turned in during the first visit.

Mental Health Assessments

Psychological Wellbeing Scale (PWB)

Participants were asked to complete an online version of the psychological wellbeing scale (PWB) (Ryff & Keyes, 1995). The PWB is an 18-item, 6-minute measurement of six subscales of wellbeing and happiness: autonomy, environmental mastery, personal growth, positive relation with others, purpose in life, and self-acceptance. They were instructed to rate how strongly they disagree or agree with each subscale on a 7-point Likert scale. The online PWB questionnaire was completed and turned in during the first visit.

Anxiety (GAD-7)

Participants were asked to complete the online version of the general anxiety disorder, 7 question screening tool (GAD-7) (Spitzer et al., 2006). The GAD-7 consists of 7 questions assessing participants anxiety. Participants answered the 7 questions on a 0-3 scale (0-"not at all"; 1-"several days"; 2-"more than half the days"; 3-"nearly every day"). The online GAD-7 questionnaire was completed and turned in during the first visit.

Fatigue (PFS)

Participants were asked to complete the online version of the Piper Fatigue Scale (PFS) (Strohschein et al., 2003). The PFS is a 27-question fatigue screening tool using a 1-10 Likert scale. Scores of 1 indicated little to no fatigue and scores of 10 indicated maximal fatigue symptoms. The online PFS questionnaire was completed and turned in during the first visit.

Quality of Life Assessment (QOL)

Participants were asked to complete the online version of the Ferrans and Powers Quality of Life Index (QOL) (Hagell & Westergren, 2006). The QOL is a 2-part questionnaire, totaling 66 questions. Part 1 of the QOL survey asked how satisfied the participant were in various

portions of their life such as “Your health”, “Your family’s health”, and “The emotional support you get from your family?” The responses from this section ranged between 1-6 with 1 indicating “Very dissatisfied” and 6 indicating “Very satisfied.” Part 2 of the QOL survey asked the participant how important various portions of their life is to them. Questions in part 2 were identical to the questions in part 1, but the responses ranged between 1-6 with 1 indicating “Very unimportant” and 6 indicating “Very important.” The online QOL questionnaire was completed and turned in during the first visit.

Leeds Sleep Evaluation Questionnaire (LSEQ)

Participants were asked to complete the Leeds Sleep Evaluation Questionnaire (LSEQ) (Tarrasch et al., 2003). The LSEQ is a 10-question visual analog scale questionnaire broken up into 4 subscales evaluating subjective measures of sleep quality including “getting to sleep,” “quality of sleep,” “awake following sleep,” and “behavior following wakening.” Participants were instructed to mark a vertical tick along a 100mm horizontal line. The LSEQ questionnaire was completed and turned in during the first visit.

Visit 2

Visit 2 was completed no less than 24 hours following the completion of the participant’s visit 1.

Anaerobic Testing

Participants were assessed in anaerobic fitness via the Wingate anaerobic power test on a cycle ergometer (Monark Ergomedic 894E, Monark, Varberg, Sweden) (Bar-Or, 1987). Participants began by cycling between 60-75 revolutions per minute (RPM) at a self-selected resistance for 5 minutes. Upon completion of the warm-up, resistance was dropped to 0, and the participant were instructed to begin pedaling at their max cadence. Once participants reached

their max pedal cadence, 7.5% of the participant's body weight were added to the cycle ergometer, and the test began. Participants cycled for a total of 30 seconds at a resistance of 7.5% body weight. At the cessation of the 30 second max test, participants cycled for an additional 5 minutes at a self-selected resistance for cool-down. Participants were assessed on peak anaerobic power, mean anaerobic power, relative peak anaerobic power, total work, and fatigue index.

Data Analysis

All subject data were collected and recorded in Microsoft Excel program. Data were analyzed using statistical package for the social sciences (SPSS) (SPSS, Inc, Chicago, III). Means and standard deviation was calculated for all major outcome variables. Data were then averaged for each group and a 3 way (group) analysis of variance (ANOVA) was used to determine whether anaerobic power, mental health and fatigue, and sleep quality were different among the groups. Significance was set at alpha=0.05.

CHAPTER IV

RESULTS

Participant Characteristics

A total of 24 participants (21 males and 3 females) were recruited and placed into groups based on their regular cannabis/CBD or non-cannabis/CBD use. There were 7 males and 1 female in the cannabis user group (CA), there were 7 males and 1 female in the cannabidiol user group (CB) and there were 7 males and 1 female in the cannabis or CBD non-user group (CO). When all groups were combined, the average age of the participants was 25.33 ± 4.34 years. The average mass, height, and BMI of all participants was 74.40 ± 10.94 kg, 172.43 ± 6.62 cm, and 24.91 ± 2.43 kg/m^2, respectively. The average lean body mass and body fat % of all participants was 62.33 ± 9.34 kg and 15.76 ± 4.56% body fat. There were no significant differences in participant demographics between groups (Table 1).

Table 1

Participant Characteristics

Characteristics	CA (n=8)	CB (n=8)	CO (n=8)
Age (years)	23.88 ± 3.31	25.13 ± 3.36	27.00 ± 5.83
Mass (kg)	77.62 ± 12.71	71.22 ± 10.16	74.36 ± 10.24
Height (cm)	172.48 ± 6.81	172.36 ± 6.96	172.44 ± 7.00
BMI (kg/m^2)	25.99 ± 3.23	23.85 ± 1.82	24.89 ± 1.75
Lean Body Mass (kg)	64.27 ± 8.68	60.21 ± 10.80	62.52 ± 9.24
Body Fat (%)	16.54 ± 4.57	14.70 ± 5.55	16.05 ± 3.82

Note. BMI = Body Mass Index; kg = kilograms; cm = centimeters; kg/m^2 = kilogram per meter squared; % = percent. Values presented as mean ± SD.

Characteristics of Cannabis and Cannabidiol Use

Cannabis

All participants in CA met the minimum use requirements of 3 or more cannabis use sessions per week for the past 8 weeks. Four participants in CA reported using cannabis products daily. The primary method of cannabis use in the CA group was vaporizers (n=8) with THC contents ranging from 15-24%. Secondary modalities of cannabis use included hand pipes (n=2) using *Cannabis* flower with THC contents ranging from 15-24% and edibles (n=2) with THC content ranging from 10-15mg. Overall, daily cannabis use ranged from 1 to 3 sessions per day while weekly use ranged from 3 to 7 days per week using cannabis products. Additionally, the duration of lifetime chronic cannabis use ranged from 1 to 12 years. Further information on the habits of cannabis users in the CA group can be found in the table below (Table 2).

Table 2

Cannabis Use Characteristics

	CA (n=8)
Days Used in the Past Week	5.6 ± 1.8
Days Used in the Past Month	23.9 ± 7.1
Daily Uses of Cannabis: Overall	2.3 ± 0.7
Daily Uses of Cannabis: Weekday	2.0 ± 0.9
Daily Uses of Cannabis: Weekend	3.1 ± 2.0
Primary Method of Use	
Method Number (n)	Vaporizer 8
Total Years Using Cannabis (years)	6.5 ± 4.0
Age at First Use (years)	16.4 ± 1.5
Age Started Using Cannabis >2 times/month (years)	18.4 ± 2.3
Age Started Using Cannabis on Daily or Near Daily Basis (years)	19.9 ± 3.0

Cannabidiol

All CBD users had been using 50mgs of CBD at least three times per week for the past 8 weeks. Overall, the participants in the CB group were consuming 1.50 ± 0.28 mg/kg of CBD that ranged from 1.09 to 1.99 mg/kg. The CBD was obtained in a pill form from 6º Wellness (©2020 6º Wellness). All products were hemp-derived, within legal limits and no reported side-effects were disclosed by the participants.

Mental Health Measures

Participant's mental health was assessed using the Psychological Wellbeing (PWB), Generalized Anxiety Disorder–7 (GAD-7), Piper Fatigue Scale (PFS), and Ferrans and Powers Quality of Life Index (QOL) surveys.

The PWB measure included six subscales Autonomy (AT), Environmental Mastery (EM), Personal Growth (PG), Positive Relations with Others (PR), Purpose in Life (PL), and Self-Acceptance (SA). The CB and CO were significantly greater in the AT (78.3%, $p<0.001$; 53.0% $p=0.003$), PG (225%, $p<0.001$; 206.3%, $p<0.001$), PR (72.4%, $p=0.001$; 71.1%, $p=0.002$), PL (61.3%, $p=0.003$; 62.5%, $p=0.003$), and SA (61.1%, $p=0.001$; 51.1%, $p=0.02$) subscales of the PWB when compared to CA (Table 3). There were no significant differences in mean PWB scores between CB and CO in all subscales ($p>0.05$). Mean PWB subscale scores for CA ranged from 7 to 15 (AT), 7 to 16 (EM), 3 to 11 (PG), 7 to 11 (PR), 5 to 15 (PL), and 7 to 18 (SA) in each subscale. Mean PWB subscale scores for CB ranged from 14 to 21 (AT), 6 to 21 (EM), 14 to 21 (PG), 11 to 21 (PR), 11 to 20 (PL), and 14 to 21 (SA) in each subscale. Mean PWB subscale scores for CO ranged from 11 to 21 (AT), 7 to 20 (EM), 13 to 21 (PG), 10 to 21 (PR), 11 to 21 (PL), and 7 to 21 (SA) in each subscale.

Table 3

Psychological Wellbeing Outcomes

PWB Subscales	CA (n=8)	CB (n=8)	CO (n=8)
Autonomy	10.38 ± 2.56*	18.50 ± 2.51	15.88 ± 3.52
Environmental Mastery	11.63 ± 2.72	16.13 ± 5.06	14.00 ± 3.78
Personal Growth	6.00 ± 2.45*	19.50 ± 2.62	18.38 ± 3.02
Positive Relations with Others	9.50 ± 1.69*	16.38 ± 3.96	16.25 ± 4.13
Purpose in Life	10.00 ± 3.70*	16.13 ± 3.09	16.25 ± 3.37
Self-Acceptance	11.25 ± 3.92*	18.13 ± 2.47	17.00 ± 4.72

Note. Values presented as mean ± SD.
*Denotes mean subscale scores were significantly higher in the CB and CO groups than the CA group ($p<0.05$)

Table 4 presents the mean scores of the GAD-7, PFS, and QOL surveys between CA, CB, and CO. There were no significant differences in mean GAD-7 scores between groups ($p=0.40$). Although not significant, the mean GAD-7 score in CA was 50.9% and 5.5% higher when compared to CB and CO, respectively. Additionally, the mean GAD-7 score in CO was 92.3% higher when compared to CB, but not statistically significant. Mean GAD-7 scores of CA, CB, and CO ranged from 0 to 16, 0 to 8, and 0 to 21, respectively.

There were no significant differences in mean PFS scores between groups ($p=0.25$). Although not significant, the mean PFS score in CA was 36.1% and 11.1% higher when compared to CB and CO, respectively. Additionally, the mean PFS score in CO was 39.0% higher when compared to CB, but not statistically significant. Mean PFS scores of CA, CB, and CO ranged from 2.23 to 6.86, 1.00 to 5.45, and 1.00 to 6.73, respectively.

Analysis of the QOL index revealed that the mean QOL score of CB was 27.0% higher than the mean score of CA ($p=0.004$), but no significant differences were found between CA and CO ($p=0.11$) or CB and CO ($p=0.48$). Although not significant, the mean QOL score of CO was 18.5% higher than CA and 6.7% lower than CB. Mean QOL scores of CA, CB, and CO ranged from 16.58 to 21.66, 21.05 to 30.00, and 14.00 to 29.53, respectively.

Table 4

Mental Health Assessment Outcomes

Mental Health Assessments	CA (n=8)	CB (n=8)	CO (n=8)
GAD-7	6.88 ± 6.06	3.38 ± 3.07	6.50 ± 6.78
PFS	4.13 ± 1.70	2.64 ± 1.55	3.67 ± 2.01
QOL	19.45 ± 2.15**	24.70 ± 3.57	23.04 ± 5.38

Note. GAD-7 = Generalized Anxiety Disorder-7; PFS = Pipers Fatigue Scale; QOL = Ferrans and Powers Quality of Life Index. Values presented as mean ± SD.
**Denotes mean QOL scores were significantly greater in the CB ($p<0.01$) group than the CA group

Perceived Sleep

Participants were evaluated on their subjective sleep quality with the Leeds Sleep Evaluation Questionnaire (LSEQ). Table 5 presents the mean scores of the LSEQ and its subscales Getting to Sleep (GTS), Quality of Sleep (QOS), Awake Following Sleep (AFS), and Behavior Following Wakening (BFW) between the CA, CB, and CO groups. Mean LSEQ scores of CA, CB, and CO ranged from 39.16 to 64.02, 46.95 to 65.88, and 41.76 to 56.59. Mean GTS scores of CA, CB, and CO ranged from 40.81 to 69.47, 42.74 to 58.43, and 42.75 to 68.24, respectively. Mean QOS scores of CA, CB, and CO ranged from 25.23 to 78.50, 12.94 to 82.35, and 30.59 to 54.71, respectively. Mean AFS scores of CA, CB, and CO ranged from 28.50 to 56.25, 35.55 to 87.06, and 20.59 to 59.41, respectively. Mean BFW scores of CA, CB, and CO ranged from 26.79 to 63.86, 47.84 to 85.88, and 26.27 to 70.20, respectively. There were no

significant differences between groups in mean LSEQ (p=0.42), GTS (p=0.44), QOS (p=0.29), AFS (p=0.14), and BFW (p=0.14) scores.

Table 5

Leeds Sleep Evaluation Questionnaire Outcomes

LSEQ Subscales	CA (n=8)	CB (n=8)	CO (n=8)
LSEQ	51.31 ± 9.66	55.37 ± 7.53	50.33 ± 6.11
GTS	57.08 ± 11.41	52.17 ± 5.26	57.71 ± 9.95
QOS	59.00 ± 16.82	49.73 ± 22.29	45.93 ± 7.55
AFS	39.97 ± 10.59	55.82 ± 23.98	40.15 ± 15.51
BFW	47.98 ± 11.27	62.04 ± 13.92	52.68 ± 15.63

Note. LSEQ = Leeds Sleep Evaluation Questionnaire; GTS = Getting to Sleep; QOS = Quality of Sleep; AFS = Awake Following Sleep; BFW = Behavior Following Wakening. Values presented as mean ± SD.

Anaerobic Power Measures

Anaerobic power outcomes are presented in Table 6. Average peak power of CA, CB, and CO ranged from 502.66 to 1003.64 W, 412.77 to 885.06 W, 540.82 to 962.40 W, respectively. Relative peak power of CA, CB, and CO ranged from 7.03 to 11.28 W/kg, 7.64 to 12.85 W/kg, and 7.16 to 11.73 W/kg, respectively. Mean power of CA, CB, and CO ranged from 350.98 to 687.19 W, 290.72 to 684.65 W, and 386.12 to 680.46 W, respectively. Relative mean power of CA, CB, and CO ranged from 5.66 to 7.95 W/kg, 5.53 to 8.48 W/kg, and 5.59 to 7.54 W/kg, respectively. Anaerobic fatigue of CA, CB, and CO ranged from 35.54 to 70.61 %, 43.72 to 66.43 %, and 40.47 to 65.07 %, respectively. There were no significant differences between the groups in terms of average peak power (p=0.77), relative peak power (p=0.15), mean power (p=0.97), relative mean power (p=0.30), and anaerobic fatigue (p=0.82).

Table 6

Anaerobic Power Outcomes

Anaerobic Measures	CA (n=8)	CB (n=8)	CO (n=8)
Average Peak Power (W)	696.43 ± 159.28	749.60 ± 152.33	711.95 ± 140.02
Relative Peak Power (W/kg)	9.03 ± 1.50	10.51 ± 1.55	9.51 ± 1.36
Mean Power (W)	519.55 ± 106.99	528.03 ± 114.10	522.58 ± 87.21
Relative Mean Power (W/kg)	6.72 ± 0.85	7.38 ± 0.96	6.97 ± 0.65
Anaerobic Fatigue (%)	55.30 ± 10.20	57.11 ± 6.39	54.41 ± 9.13

Note. W = Watts; W/kg = Watts per kilogram; % = percent. Values presented as mean ± SD.

CHAPTER V

DISCUSSION AND CONCLUSIONS

The purpose of this study was to determine whether there are differences among groups of individuals who regularly use cannabis, cannabidiol (CBD), or who are non-users with respect to mental health, sleep, and anaerobic power measures. Given the easy access to cannabinoid products and the lack of information on the impact of cannabinoids on the body, further research exploring the effects of cannabinoids on overall health and wellbeing is paramount for informed, safe, and effective utilization of these products. The present study demonstrates no significant differences between CA, CB, and CO with respect to measures of anxiety, subjective fatigue, perceived sleep quality, and anaerobic power, but revealed significant differences between CA and both CB and CO in measures of psychological wellbeing and quality of life. These results suggest that regular cannabis users may have a lower psychological state and lower perceived quality of life when compared to CBD users or cannabis and CBD non-users.

Mental Health Measures

Globally, over 260 million people suffer from some form of mood disorder leading to decreased quality of life outcomes, reductions in mood, and impaired ability to perform daily activities (García-Gutiérrez et al., 2020). Anxiety and depression are two of the most common mental health concerns in our society and often, go undiagnosed and untreated (Trudgen & Lawn, 2011). When untreated, these mood disorders can be debilitating and interfere with daily functioning and quality of life. This leaves individuals seeking out treatment on their own. The

legalization of cannabis and its increased accessibility are worrisome due to the lack of cannabinoid research in healthy populations and the possible risks associated with cannabis use.

Anxiety

In the present study, perceived anxiety was assessed with the Generalized Anxiety Disorder–7 (GAD-7) survey and there were no significant differences in the mean GAD-7 scores between the CA, CB, or CO groups ($p=0.40$). In the literature, a general cut-off of 8 on the GAD-7 has a sensitivity of 92% and specificity of 76% for the diagnosis of generalized anxiety disorder (Plummer et al., 2016). Although all three groups had mean GAD-7 scores below this benchmark suggesting the lack of significant anxiety symptoms, there were some outliers among participants. One of the participants in CO had a GAD-7 score of 21 which would classify them as having severe anxiety. This is concerning due to the small sample size which undoubtedly increased the mean GAD-7 scores of the CO. Additionally, there were 3 participants in the CA that had GAD-7 scores greater than 12 which would also classify them as having moderate anxiety and likewise increasing the mean GAD-7 scores of the CA. The presence of these outliers that were greater than one standard deviation from the average is concerning, but not atypical in a college-aged population where the prevalence of anxiety disorders is high (Kitzrow, 2003). Initially, it was hypothesized that

H1 Cannabis and CBD users will have higher assessments of mental health and sleep and lower anaerobic power capability when compared to non-users.

However, the results of the present study contradicted our original hypothesis and suggests that there are no significant differences between regular cannabis users or CBD users compared to non-users in measures of perceived anxiety. This would indicate that regular cannabis or CBD use does not significantly affect perceived anxiety in healthy and physically active populations.

The anxiolytic properties of cannabis and THC have been investigated in the literature and the results are somewhat inconsistent. Most research related to anxiety is with individuals with mental health disorders. It is important to note that patients with anxiety disorders also have high rates of cannabis and THC use and these findings did not indicate that cannabis use is associated with developing the anxiety disorders (Crippa et al., 2009). In fact, this relationship may be explained by the notion that many people suffering from anxiety often use recreational cannabis and THC products for its euphoric effects. These effects are often accompanied by a decrease in anxiety and an increase in sociability (Saugy et al., 2006). Conversely, cannabis and THC use is also linked to the development of severe anxiety, paranoia, panic, and psychosis (Ashton, 2001). These contradicting findings may be explained by the fact that cannabis contains both THC and CBD. THC is associated with the euphoric feelings experienced by users (Lucatch et al., 2018) while CBD functions as the main anxiolytic compound (Zuardi et al., 2017). The results of these studies suggest that the combination of THC and CBD may cause less perceivable changes to anxiety when compared to using CBD by itself. This notion is further corroborated by the fact that CBD functions as a CB1 antagonist, a non-competitive allosteric modulator of CB2, and indirectly diminishes the efficacy of THC (Laprairie et al., 2015).

Additionally, from 1995 to 2014, the average THC content of cannabis products has drastically increased by almost three-fold from 4% to approximately 12%, while the average CBD content of cannabis has decreased from 0.28% to less than 0.15% (ElSohly et al., 2016). This reduction in CBD and increase in THC content in current recreational cannabis could also contribute to the contradictory effects of cannabis on anxiety. Furthermore, the primary method of cannabis use in the current study were vaporizers which use cartridges containing cannabis oil, which is high in THC, ranging from 15-24%, and low in CBD content which may also

contribute to the lack of significant differences in anxiety when compared to the CO or CB (Guo et al., 2021).

The lack of significant differences in anxiety in CB compared to CO contradicts the notion that CBD can function as an anxiolytic compound (Blessing et al., 2015). This lack of difference between the CB and CO could be attributed to the sample size of the study and lack of standardized CBD dosages. Cannabidiol is not well regulated and is publicly accessible in locations like gas stations or supermarkets. In the literature, CBD has anxiolytic and functions which act in an inverted U-shaped dose-dependent manner (Zuardi et al., 2017). In this particular study, participants were given dosages of 100mg, 300mg, and 900mg of CBD prior to a public speaking test and the 300mg dosage significantly decreased anxiety scores while the 100mg and 900mg dosages failed to significantly change anxiety (Zuardi et al., 2017). Given this information, it is clear that future research would benefit from standardized CBD dosages of around 300mg to facilitate CBD's effectiveness on treating anxiety.

Depression

Although not investigated in this study, depression is another mental health disorder to consider due to its high prevalence and relationship with anxiety. Anxiety and depression are highly comorbid, with anxiety presenting prior to the development of depression (Kalin, 2021). Depression is a mental health disorder characterized by chronic feelings of sadness, emptiness, or irritability, accompanied with changes in an individual's ability to function normally (American Psychiatric Association, 2022). Depression and depressive disorders are part of a global mental health crisis with a lifetime prevalence of 20%-25% in women and 7%-12% in men (World Health Organization, 2002). Furthermore, patients experiencing depression have a higher risk of engaging in suicidal behaviors (Hawton et al., 2013), which is further corroborated

by the fact that 50% of suicide victims meet the diagnostic criteria for a depressive disorder (Joiner et al., 2005; McGirr et al., 2007). A few of the various risk factors for depression include substance abuse (Coelho et al., 2000), childhood trauma (Martins-Monteverde et al., 2019), and family history of depression (Hodgson & McGuffin, 2012). Given these findings, depression is an important psychiatric condition to screen for and treat at the first sign of symptoms (Jeon, 2011).

Current literature suggests that THC use and depression may have a significant correlation. A meta-analysis concluded that chronic or heavy THC use is associated with an increased risk of depressive disorders (Lev-Ran et al., 2014). These results were further supported by another study which found that depression was positively and significantly associated with THC use (Dierker et al., 2018). Additionally, a recent survey of 281,650 young adults aged 18–34 years revealed that THC use was positively associated with increased risk of suicidal ideation, planning, and attempts (Han et al., 2021). However, two population-based longitudinal studies suggest that THC use, even chronic THC use, was not associated with an increased incidence of major depressive disorders, after controlling for baseline confounders (Danielsson et al., 2016; Feingold et al., 2015). The literature is currently undecided on whether THC use is associated with developing depression, thus further investigation is warranted.

There is some evidence which supports the use of CBD to alleviate depressive symptoms. In mouse models, intravenous injection of 10mg/kg or oral administration of 100mg/kg of CBD resulted in antidepressant behavioral effects during a forced swim test (Xu et al., 2019). In human models, one study with twenty chronic cannabis users found that daily oral ingestion of 200mg of CBD decreased depressive and psychotic-like symptoms and improved attention, memory, and verbal learning when compared to baseline (Solowij et al., 2018). In addition, a

survey of 1483 subjects who used CBD daily revealed that 400 subjects used CBD for mood-improvement effects with positive results (Corroon & Phillips, 2018). However, this study did not differentiate between synthetic or natural CBD-products, thus the CBD-product used may have contained THC as well. Due to the availability of unregulated CBD-products, further investigation is warranted before CBD can be considered a safe and effective treatment for depression.

Psychological Wellbeing

In the present study, mean PWB scores in five of the six subscales were significantly higher in both the CB ($p<0.01$) and CO ($p<0.05$) when compared to the CA. However, there were no significant differences when comparing mean PWB scores between the CB and CO ($p>0.1$). Although there is no global standardization of scores published by the creators of the PWB, higher scores for each subcategory indicate that the participant has a mastery of this area in their life while a lower score indicates that the participant is uncomfortable with this same area (Ryff & Keyes, 1995). The results of the present study indicate that frequent cannabis use was associated with lower scores of psychological wellbeing when compared to frequent CBD use or non-use. Initially, it was hypothesized that

H1 Cannabis and CBD users will have higher assessments of mental health and sleep and lower anaerobic power capability when compared to non-users.

This assertion was made due to the reported euphoric effects of cannabis and THC (Lucatch et al., 2018) and the protective effects of CBD with respect to psychosis (Bloomfield et al., 2020) and anxiety (Zuardi et al., 2017). However, the results of the present study indicate that individuals regularly consuming CBD may not have higher levels of psychological wellbeing when compared to non-users. Conversely, regular cannabis use may be associated with decrements in psychological wellbeing when compared to regular CBD use or non-use. Finally,

overall psychological wellbeing might have been lower during this past year because of major global events like the coronavirus-19 pandemic or the Russia-Ukraine War.

Fatigue

The Piper Fatigue Scale (PFS) was utilized to assess the participants' perceived fatigue and the results revealed no significant differences in mean PFS scores among CA, CB, and CO ($p=0.25$). These results refute our original hypothesis that

> H1 Cannabis and CBD users will have higher assessments of mental health and sleep and lower anaerobic power capability when compared to non-users.

Although these results were not statistically significant, it does suggest that regular cannabis or regular CBD use does not detrimentally affect measures of perceived fatigue when compared to non-use. Additional analysis revealed that the mean fatigue score for all participants was 3.48 ± 1.80 which placed them in the moderate severity category. The mean scores of the CA, CB, and CO groups was 4.13 ± 1.70, 2.64 ± 1.55, and 3.67 ± 2.01, respectively, which placed CA and CO in the moderate severity category and the CB in the mild severity category. These results suggest that the participants in all three groups were experiencing fatigue, but this finding is not atypical in a university-based population. In fact, fatigue is highly prevalent in undergraduate students. One study with 287 undergraduate students reported that 87% of students experienced mild fatigue symptoms (Nyer et al., 2015). These findings were corroborated in another study of 189 undergraduate nursing students, which found that 85.3% of students reported feeling moderately to extremely tired (Amaducci et al., 2010). Due to the academic and social stress that college students face, the high levels of fatigue indicated in this study may represent the functional state of these individuals.

Cannabis improves ratings of chronic fatigue in patients suffering from Parkinson's disease and multiple sclerosis (Kindred et al., 2017), chronic pain (Safakish et al., 2020), and

cancer (Anderson et al., 2019). On the other hand, the most commonly reported symptom of cannabis use is fatigue (Shannon et al., 2019). Additionally, a lack of motivation and laziness is also associated with cannabis use (Pacheco-Colón et al., 2018). However, it is important to distinguish between the two commercially available phenotypes of cannabis, *Cannabis sativa* and *Cannabis indica*. Although both phenotypes contain THC and CBD, their ratios of THC and CBD are different. *C. sativa* contains a higher ratio of THC:CBD, while *C. indica* contains a lower ratio of THC:CBD (McPartland, 2018). In other words, *C. indica* strains produce greater amounts of CBD when compared to *C. sativa*. This phytochemical difference also distinguishes the effects of each phenotype on human physiology with *C. sativa* strains associated with euphoric, hallucinogenic, and pain-relieving effects while *C. indica* is associated with relaxation and stress relief (Hazekamp & Fischedick, 2012). It is accepted that *C. indica* is the phenotype of cannabis that is associated with increased subjective fatigue due to its relaxation properties. This fatigue may be a side-effect of its higher CBD content when compared to *C. sativa* (Hazekamp & Fischedick, 2012). This distinction may explain why fatigue is the most commonly reported side-effect of cannabis use. However, it is important to note that in the previous studies mentioned, there was no information about the strains of cannabis that were used. Therefore, it is imperative that future studies distinguish and standardize the type cannabis used and its THC:CBD content in order to further elucidate the effects of cannabis on mental and physiological parameters.

In the current literature, there are very few studies investigating isolated THC and its effects of fatigue. In one study with 1,120 cancer patients, 300 subjects reported a 30% improvement to subjective fatigue following 4 months of at home THC use (Anderson et al., 2019). However, in this study, the participants were using THC products that contained varying

amounts of CBD which confounds the effects of pure THC use and may instead be representative of typical cannabis products. Due to the lack of research conducted with THC products, it is still unclear as to the effects of THC on human mental and physiological parameters. Therefore, further research is necessary to elucidate the effects of THC on fatigue.

The effectiveness of CBD as a treatment for alleviating fatigue is currently undecided. In one study with 371 subjects with autoimmune hepatitis, 38% of patients reported using CBD for fatigue with 61% of these respondents reporting significant improvements in subjective fatigue (Mathur et al., 2020). Conversely, another study found that 5mg/kg oral administration of CBD was not significant in improving subjective fatigue in physically active individuals when compared to a placebo (Crossland et al., 2022). This divide in findings on the effectiveness of CBD in improving fatigue is prevalent throughout the literature, therefore further investigation is warranted before determining if CBD is a safe and effective treatment for fatigue.

The results of the current study further contribute to the contradictory literature on the effectiveness of cannabis and CBD on fatigue. However, the lack of statistical difference between mean PFS scores in CA and CB when compared to CO may also indicate that cannabis and CBD use is not related to perturbations in perceived fatigue in healthy and active populations. Due to the multi-factorial nature of fatigue, further investigations into the complex effects of cannabinoids on the psychological and physiological mechanisms of fatigue are warranted.

Quality of Life

Quality of life was assessed using the Ferrans and Powers QOL index and the results revealed that mean QOL scores were significantly higher in CB when compared to CA ($p=0.004$), but not between CA and CO ($p=0.11$) and CB and CO ($p=0.48$). The mean QOL

scores for all participants was 22.40 ± 4.37 which placed them in the moderately satisfied category (Suleiman et al., 2017). The mean scores of the CA, CB, and CO groups were 19.45 ± 2.15, 24.70 ± 3.57, and 23.04 ± 5.38, respectively, which placed the CA and CO in the slightly satisfied category and the CB in the moderately satisfied category (Suleiman et al., 2017). Although the overall scores revealed a moderate satisfaction in quality of life measures, the results suggest that CBD users have a higher perceived quality of life when compared to cannabis users. These results contradict our initial hypothesis that

> H1 Cannabis and CBD users will have higher assessments of mental health and sleep and lower anaerobic power capability when compared to non-users.

But it is important to note that the lack of significance in mean QOL scores between CA and CO as well as CB and CO suggest that regular cannabis or CBD use does not significantly affect perceived quality of life when compared to non-use. However, the present study compared cannabis and CBD use in healthy and physically active populations, which may have contributed to the high quality of life scores. Furthermore, previous CBD intervention studies have mainly focused on populations with chronic diseases. Consequently, their quality of life is actively hindered by their chronic ailments which allows for a greater chance to detect any change in this measure (Capano et al., 2020).

Although not indicated in this study, heavy cannabis or THC use is associated with lower QOL scores, but it is unknown as to whether heavy cannabis use causes reduced QOL scores or whether a low QOL facilitates heavy cannabis use (Goldenberg et al., 2017). However, another recent study with 7405 Brazilian adults, of which 6620 were cannabis users and 785 non-users, found that habitual and occasional cannabis users had higher QOL scores when compared to non-users (Morais et al., 2022). These previous studies have highlighted the contradictory nature

of cannabinoid research, thus further investigation is warranted especially in healthy and active populations.

Sleep

Sleep is an important physiological tool and plays a vital role in maintaining both brain function and systemic physiological functioning (Medic et al., 2017). The necessity of adequate sleep is paramount to the maintenance of overall health and wellbeing and the lack of sleep and poor sleep quality is linked to the development of many chronic diseases such as diabetes and heart disease (Gottlieb et al., 2005; Wolk et al., 2005), as well as mental health disorders such as depression and anxiety (Franzen & Buysse, 2008). These complications are further exacerbated in a college-aged population where it is estimated that up to 60% of college students report poor sleep quality and daytime sleepiness (Lund et al., 2010). Although the current recommendation for adults aged 18-60 years is to sleep for 7 or more hours, it is estimated that one-third of adults in the United States do not meet this recommendation (Watson et al., 2015).

Perceived sleep quality was assessed using the LSEQ and its subscales GTS, QOS, AFS, and BFW and there were no significant differences among mean scores of the GTS ($p=0.44$), QOS ($p=0.29$), AFS ($p=0.14$), and BFW ($p=0.14$) subscales among CA, CB, and CO. There is currently no standard scoring classification for subjective sleep quality for the LSEQ. Therefore, comparison among the three groups in this study is paramount in determining whether cannabis, CBD, or non-use is linked to significant differences in subjective sleep quality. Initially, it was hypothesized that

> H1 Cannabis and CBD users will have higher assessments of mental health and sleep and lower anaerobic power capability when compared to non-users.

However, the results of the present study suggest that measures of subjective sleep quality are not significantly different between cannabis users, CBD users, and non-users. These findings

further confound the current literature which is currently split on the effectiveness of both cannabis and CBD as a sleep aid in improving subjective sleep quality.

In the literature, cannabis flower has positive effects on measures of sleep which include decreased sleep onset latency (Cousens & DiMascio, 1973) and wakefulness after sleep onset (Pivik et al., 1972), while other studies reported negative effects including decreased REM (Feinberg et al., 1976) and increased slow wave sleep (Barratt et al., 1974). The obscure effectiveness of cannabis on sleep in the current literature becomes further convoluted due to the significant role the endocannabinoid system plays in the regulation of the circadian sleep-wake cycle and the maintenance and promotion of sleep (Sanford et al., 2008; Vaughn et al., 2010). Although cannabis and cannabinoids play a major role in the circadian sleep-wake cycle, the current literature is undecided on whether cannabis improves or inhibits sleep quality.

The results of the present study are surprising as both THC and CBD affect sleep architecture such as the stages of sleep (Nicholson et al., 2004) and measures of sleep including sleepiness (Carley et al., 2018) and subjective sleep quality (Nicholson et al., 2004), but were not replicated in this investigation. Although not revealed in this study, THC improves subjective sleep quality. Such is the case in two studies which found that ingestion of 10 mg of dronabinol, which is a synthetic form of THC, resulted in increased subjective sleep quality and decreased subjective sleepiness (Bedi et al., 2010; Carley et al., 2018). However, chronic administration of THC decreases overall sleep duration and sleep efficiency while increasing sleep onset latency, which may be a result of increased tolerance related to repeated THC use (Kaul et al., 2021). On the other hand, oral ingestion of 15 mg of CBD decreases subjective sleep quality and increases wakefulness in young adults (Nicholson et al., 2004). However, another study of 72 adults revealed that dosages of 25 mg/d to 175 mg/d of CBD taken daily improved subjective sleep

scores in the first month of treatment, but these scores fluctuated throughout the 3-month investigation (Shannon et al., 2019). It is likely that both THC and CBD are dose-dependent and further investigation into effective dosages and methods of administration are warranted before THC or CBD can be utilized as an effective sleep aid.

The results of the present study may have been confounded by the healthy and active participants. Moderate physical activity improves subjective sleep quality both acutely and chronically (F. Wang & Boros, 2021). Additionally, the presence and number of chronic diseases including arthritis and osteoporosis are also positively associated with lower scores of subjective sleep quality (Hsu et al., 2021). Future studies may want to further explore the effects of cannabis and CBD in a wide variety of both healthy and diseased populations.

Anaerobic Measures

Fatigue is a subjective term used to describe feelings of tiredness, lack of energy, and exhaustion (Krupp & Pollina, 1996). There are many different facets of fatigue such as muscular fatigue, chronic fatigue, and psychological fatigue that could be caused by exertion, chronic diseases, and psychiatric conditions. Consequently, fatigue is multifactorial and can be caused by both physiological and psychological factors. In the context of exercise and physical activity, muscular fatigue is the facet of fatigue most evaluated. Muscular fatigue can be defined as a decrease in the maximal force or power that the associated muscles can produce during a bout of sustained exercise and occurs from the onset of the exercise. (Enoka & Duchateau, 2008). Metabolically, this decrease in performance and power could be attributed to the depletion of metabolites such as adenosine triphosphate (ATP) or phosphocreatine (PCr). ATP is the main energy provider in the body and plays a pivotal role in initiating and sustaining muscle

contractions during physical activity, while PCr is a rapid regenerator of ATP and plays a role during short duration, high intensity exercises such as a Wingate Test (Bonora et al., 2012).

In the present study, measures of anaerobic fitness were facilitated with the Wingate protocol using a cycle ergometer and the results revealed no significant differences among CA, CB, and CO with respect to average peak power ($p=0.77$), relative peak power ($p=0.15$), mean power ($p=0.98$), relative mean power ($p=0.30$), and anaerobic fatigue ($p=0.82$). When classified by gender, average peak power for CA, CB, and CO was 724.11 ± 149.82 W, 797.72 ± 73.89 W, and 736.40 ± 131.51 W respectively, for males and 502.66 W, 412.77 W, and 540.82 W for the three female participants. These results would classify the males of CA and CO in the 60th percentile and the CB in the 80th percentile of young adults (Maud & Shultz, 1989). The female of CA would be classified in the 65th percentile, the female in CB in the 30th percentile, and the female in CO in the 85th percentile (Maud & Shultz, 1989).

Relative peak power for CA, CB, and CO was 9.04 ± 1.63 W/kg, 10.92 ± 1.11 W/kg, and 9.51 ± 1.47 W/kg respectively, for males and 8.98 W/kg, 7.64 W/kg, and 9.55 W/kg for the three female participants. These results would classify the males in the CA in the 45th percentile, the CB in the 90th percentile, and the CO in the 55th percentile of young adults (Maud & Shultz, 1989). The female of the CA would be classified in the 85th percentile, the female in CB in the 50th percentile, and the female in CO in the 95th percentile of young adults (Maud & Shultz, 1989).

Mean power for the CA, CB, and CO groups was 543.63 ± 89.12 W, 561.93 ± 66.81 W, and 542.07 ± 72.98 W, respectively, for males and 350.98 W, 290.72 W, and 386.12 W for the three female participants. These results would classify the males of the CA and CO in the 35th percentile and the CB in the 45th percentile of young adults (Maud & Shultz, 1989). The female

of CA would be classified in the 25th percentile, the female of CB in the 10th percentile, and the female of CO in the 55th percentile of young adults (Maud & Shultz, 1989).

Relative mean power for the CA, CB, and CO groups was 6.78 ± 0.90 W/kg, 7.66 ± 0.57 W/kg, and 6.99 ± 0.70 W/kg respectively, for males and 6.27 W/kg, 5.38 W/kg, and 6.82 W/kg for the three female participants. These results would classify the males of CA and CO in the 25th percentile and CB in the 60th percentile of young adults (Maud & Shultz, 1989). The female of CA would be classified in the 45th percentile, the female of the CB in the 10th percentile, and female in the CO in the 70th percentile (Maud & Shultz, 1989).

Anaerobic fatigue for the CA, CB, and CO groups was 54.82 ± 10.93 %, 57.25 ± 6.98 %, and 53.78 ± 9.66 %, respectively, for males and 58.59 %, 56.14 %, and 58.86 % for the three female participants. These results would classify the males of CA and CO in the 90th percentile and CB in the 95th percentile of young adults (Maud & Shultz, 1989). The females of the CA, CB, and CO would be classified in the 95th percentile of young adults (Maud & Shultz, 1989).

Although no significant differences were found among CA, CB, and CO groups with respect to these anaerobic measures, CB had a 3% higher anaerobic performance on the Wingate test, which is meaningful, although this difference failed to reach statistical significance. However, these results contradict our initial hypothesis that

> H1 Cannabis and CBD users will have higher assessments of mental health and sleep and lower anaerobic power capability when compared to non-users.

This would suggest that regular cannabis or CBD use does not significantly affect anaerobic power generation when compared to non-users in healthy and physically active populations. But, due to the lack of female participation, the results are currently skewed to represent a male population. Thus, further investigation into gender differences should be warranted when examining chronic use of cannabis and CBD products and their effects on anaerobic measures.

There are currently no intervention studies that have explored the direct effects of THC and CBD on anaerobic power, but there are studies that have examined the anaerobic differences between cannabis smokers and non-smokers. One study from our lab revealed no differences in anaerobic measures between cannabis smokers and non-smokers (Lisano et al., 2019), while another study found that female cannabis smokers had less power generation in the first two stages of the Wingate protocol, but significantly less anaerobic fatigue when compared to non-smokers (Lisano et al., 2023). Further exploration is warranted in order to elucidate perceivable differences between cannabis and CBD users with respect to anaerobic power measures. Additionally, future studies should explore acute cannabinoid use prior to anaerobic measurements.

Limitations

There are several limitations of the present study that should be discussed. One limitation of this study is the small sample size of 24 participants with 8 subjects per group. Due to the small sample size, it is likely that significant differences between groups were not detectable but could be revealed with a larger sample size. Additionally, another limitation was that only one female was recruited into each of the three groups, thereby creating an unbalanced data set that may be more representative of the male demographic rather than a heterogenous population. It is possible that additional female representation may reveal further differences in the examined parameters and thus should be necessitated in future iterations of this study.

Another limitation of this study is the lack of control for cannabis utilization. Subjects were permitted into the study if they were using cannabis products 3 times a week for the past 8 weeks. There was no control for the dosage, frequency, and method of use, thus the non-standardized protocol may have influenced the current results. Due to the vast difference in

cannabinoid composition of cannabis products such as the THC to CBD ratio, a standardized protocol would undoubtedly allow for further control and validity.

Finally, the current study was conducted during the spring semester of 2022 at the University of Northern Colorado during which time the Coronavirus-19 pandemic was still prevalent along with the initiation of the Russia-Ukraine War in Europe. Both global events could have affected the mental wellbeing of the participants and could have influenced the results of the mental health assessments conducted in this study.

Conclusion

Findings from this study provide a novel insight into the mental health, subjective sleep, and anaerobic power measures of regular cannabis users, regular CBD users, and a group of non-users. Although there were no significant differences among groups in terms of anthropomorphic characteristics, anxiety, fatigue, subjective sleep quality, and anaerobic power measures, there was evidence to support differences among these groups with respect to PWB and QOL measures. Initially, it was hypothesized that

H1 Cannabis and CBD users will have higher assessments of mental health and sleep and lower anaerobic power capability when compared to non-users.

However, the results of the present study revealed that cannabis users had significantly lower PWB scores when compared to both CBD and non-users, while CBD users had significantly higher QOL scores when compared to cannabis users. The cause of the difference in PWB scores is concerning as acute cannabis and THC use causes feelings of euphoria and relaxation (Hua et al., 2016), but it is possible that chronic cannabis use may deteriorate mental health and wellbeing. Conversely, the significant differences between the CB and CA groups may indicate that CBD use is more beneficial in protecting mental health and wellbeing and would be a better naturopathic alternative to cannabis. The differences in QOL scores between the CA and CB

groups may also suggest that CBD is more beneficial than cannabis in maintaining subjective quality of life, but the lack of significant differences between both the CA and CO and the CB and CO groups suggests that utilizing cannabis or CBD may not directly affect quality of life measures significantly. Overall, these results suggest that regular cannabis users may have a lower psychological state and a lower perceived quality of life when compared to CBD users or cannabis and CBD non-users. Further exploration into the effects of cannabis and CBD on healthy and active populations is warranted. Future directions for research should involve larger clinical trials with controlled doses of well characterized cannabinoid compounds.

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APPENDIX A

INSTITUTIONAL REVIEW BOARD APPROVAL

UNIVERSITY OF
NORTHERN COLORADO

Institutional Review Board

Date:	03/28/2022
Principal Investigator:	Laura Stewart
Committee Action:	**APPROVED – Renewal with Amendment**
Action Date:	03/28/2022
Protocol Number:	2101020795R001
Protocol Title:	Cannabis, Nicotine, and Inflammation Study
Expiration Date:	03/24/2023

Based on the information submitted, your study is currently: Active - Open to Enrollment. The University of Northern Colorado Institutional Review Board (IRB) for the protection of human subjects has reviewed and approved your renewal with amendment application.

As a reminder, all research must be conducted in accordance with the procedures outlined in your approved protocol.

This approval extends your expiration to the date listed above and approves the following amendments to your protocol:

We'd like to renew this study for another year. We haven't recruited subjects yet and have removed 2 study recruitment groups (CBD users only and healthy, non cannabis users). We also need approval to compensate our study participants for their time. ($40 Visa Gift Card).

- General Info
- Add/Modify Attachments
- Subjects
- Protocol Permissions

This project will continue to require renewal on an annual basis for as long as the research remains active. 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.

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

UNIVERSITY OF
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Institutional Review Board

- 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,

Michael Aldridge
IRB Co-Chair, University of Northern Colorado: FWA00000784

Silvia Correa-Torres
IRB Co-Chair, University of Northern Colorado: FWA00000784

APPENDIX B

INFORMED CONSENT

UNIVERSITY OF
NORTHERN COLORADO

CONSENT FORM FOR HUMAN PARTICIPANTS IN RESEARCH

Title: Cannabis, CBD, and Inflammation Study (CCI)

Researcher: Laura K. Stewart, Ph.D., Professor, School of Exercise and Sport Science
Phone: 970-351-1891 or 970-413-3119

Student Researchers: **Keola Tamanaha**, MS Student, School of Exercise and Sport Science
Email tama0232@bears.unco.edu

PURPOSE

Chronic inflammation, which is defined as a persistent, low-grade inflammatory response within the body, is associated with many of the negative health conditions which are prevalent in our society today. It is most well-known for its role in the progression of diseases including obesity, metabolic syndrome, cancer, cardiovascular disease, and is linked to many of the underlying factors associated with disease development including perturbations in sleep, and mental health status such as depression, anxiety, fatigue, and quality of life.

Cannabis has been used both recreationally and therapeutically to normalize behaviors of appetite, nausea, and pain. However, there is still much to learn of the therapeutic effects of cannabis. While THC is considered the most recognized component of cannabis, CBD is most associated with its use as a treatment for epilepsy, anxiety, and psychoses, and has been proposed to improve aspects of sleep, mental health, and quality of life.

The goal of this study is to investigate regular cannabis users in terms of immunological biomarkers, body weight and height assessments, body composition, surveys and questionnaires addressing cannabis use, physical activity, mental health, and sleep quality, as well as anaerobic power and fatigue.

Data Collection Procedures

Visit 1: Informed Consent, Blood Draw, Body Size and Composition, Questionnaires.

Informed Consent

Upon arrival to visit 1, you will be given the Informed Consent form and given time to review the document. The investigator will explain the experimental protocol and answer any questions you may have. You and the researcher will sign two copies of the informed consent (one for the you to take; the other for the researcher's records) if you are willing to participate in the study.

Initials: _____

Medical Health History + Physical Activity Questionnaires
You will complete a Medical History Form and a Physical Activity Readiness Questionnaire (PAR-Q). The above screening form and questionnaire are designed specifically with your health in mind by allowing the researchers to become aware of any potential health issues that might be exacerbated by physical activity.

You will be asked to complete additional questionnaires in varying length, but none will take longer than 7-10 minutes. You will be assessed on your marijuana use, current physical activity levels, as well as your feelings related to depression, anxiety, fatigue, quality of life, and sleep.

Blood Draw
Approximately 30 mL of blood will be taken via venipuncture and will be used to measure various immune markers. All blood samples will be collected with you in a fasted state between the hours of 0600-01000. During the blood draw, you will donate approximately 30ml of an intravenous blood sample.

Body Size and Composition
Height and weight will be obtained using a stadiometer SECA 220 (Chino, California, USA) and the Detecto standing digital scale (Webb City, Missouri, USA), respectively. Body composition, lean body mass (LBM) and body fat percentage (BF%) will be evaluated using air displacement plethysmography with a BODPOD (COSMED USA Inc., Concord, CA). You will be instructed to remove your shoes, socks, jewelry, and all additional clothing other than your base layer. You will then be given a swim cap to wear, and body composition analysis will be performed via manufacturers guidelines.

Structured Exercise Assessment
You will also be instructed to complete a few questions about your physical activity/structured exercise. Questions will ask you to include all physical activity completed over the week including but not limited to walking, running, swimming, or any physical activity completed during this week. You will be asked to log intensity, load, weight lifted, and any other details involved in the frequency, intensity, time, and technique of the activity.

Marijuana Use Assessment (For Cannabis Use Group Only)
Participants will complete the Daily Sessions, Frequency, Age of Onset, and Quantity of Cannabis Use Inventory *(DFAQ-CU)*. The DFAQ-CU is a 33-item questionnaire that includes items related to smoking rate, quantity, mode, and context of use, among other use patterns. The questionnaire will be completed and turned in during the first visit.

Mental Health Assessments (well-being, anxiety, fatigue, quality of life, sleep)

Psychological Wellbeing
You will be asked to complete the psychological wellbeing scale (PWB). The PWB is an 18-item, 6-minute measurement of six aspects of wellbeing and happiness: autonomy, environmental mastery, personal growth, positive relation with others, purpose in life, and self-acceptance. You will rate how strongly you agree or disagree with each subscale on a 7-point Likert scale.

Initials: _____

Anxiety
You will be asked to complete the online version of the *general anxiety disorder*, 7 question screening tool (GAD-7) [36]. The GAD-7 consists of 7 questions assessing your anxiety, answering the 7 questions on a 0-3 scale (0-"not at all"; 1-"several days"; 2-"more than half the days"; 3-"nearly every day").

Fatigue
You will be asked to complete the online version of the Piper Fatigue Scale (PFS) [37]. The PFS is a 27-question fatigue screening tool using a Likert based system (1-10) with 1 indicating little to no fatigue and 10 indicating maximal fatigue symptoms. Sample questions of the PFS are as follows; "To what degree would you describe the fatigue which you are experiencing no as being?" and, "How would you describe the degree of intensity or severity of the fatigue which you are experiencing now?"

Quality of Life Assessment
You will be asked to complete the online version of the Ferrans and Powers Quality of Life Index (QOL). The QOL is a 2-part questionnaire, totaling 66 questions. Part 1 asks how satisfied you are in various portions of your life including but not limited to; "Your health", "Your family's health", and "The emotional support you get from your family?" Available responses range between 1-6 with 1 indicating "Very dissatisfied" and 6 indicating "Very satisfied." Part 2 of the QOL asks you how important various portions of your life is to you. Questions in part 2 are identical to the questions in part 1, but the available responses range between 1-6 with 1 indicating "Very unimportant" and 6 indicating "Very important."

Sleep Evaluation Questionnaire
You will be asked to complete the *Leeds Sleep Evaluation Questionnaire* (LSEQ)[39]. The LSEQ is a 10-question visual analog scale questionnaire broken up into 4 sections assessing "getting to sleep," "quality of sleep," "awake following sleep," and "behavior following wakening." You will be instructed to mark a vertical tick along a 100mm horizontal line.

Visit 2: Anaerobic Fitness Assessment (Separated from Visit 1 by at Least 24 Hours)

You will complete an anaerobic fitness assessment using the Wingate anaerobic power test on a cycle ergometer (Monark Ergomedic 894E, Monark, Varberg, Sweden). You will begin by cycling between 60-75 revolutions per minute (RPM) at a self-selected resistance for 5 minutes. Upon completion of the warm-up, resistance will be reduced to 0, and you will be instructed to begin pedaling at your max cadence. Once you reach your max pedal cadence, 7.5% of your body weight will be added to the cycle ergometer, and the test will begin. You will cycle for a total of 30 seconds at a resistance of 7.5% body weight. At the cessation of the 30 second max test, you will cycle for an additional 5 minutes at a self-selected resistance for cool-down. You will be assessed on peak anaerobic power, mean anaerobic power, relative peak anaerobic power, total work, and fatigue index.

Initials: _____

Risk and Discomfort

There may be some minor discomfort associated with blood draws and testing**.** You will be seated comfortably during blood sampling. Any discomfort will be minimized by having a trained nurse or phlebotomist perform the blood draws. As with any exercise test, there is a chance that you will experience some discomfort including muscle soreness, fatigue, or even injuries such as sprains or strains and, or serious illness and death. You will be encouraged to stop any test at any time if there is discomfort beyond your comfort level.

Participation in this study entails minimal risk. There is a risk of bruising and a remote risk of infection with the blood sampling techniques. You may also become lightheaded and faint during these procedures. These risks will be minimized by having trained technicians using sterile, single use supplies for blood sampling. You will also be seated during blood sampling. Fruit juice will also be on hand in the event of a low blood sugar situation. As with any exercise testing, there is a chance that you will experience muscle soreness, fatigue, or even injuries such as sprains or strains. There is also a remote risk of a heart attack or stroke and in very rare cases, death. Precautions to minimize this risk have been taken by the completion of a health history questionnaire and PAR-Q.

Participation Benefits

You will be provided with a $35 VISA Gift Card upon successful completion of the study (limited to the first 12 participants). You will also be given body composition analysis and anaerobic capacity (Wingate) evaluations at no cost (valued at $400). Additionally, you will be provided with maximal strength testing and anaerobic fitness analysis. You will be provided with all your individual performance results at the end of the study.

Confidentiality

We will be assessing your marijuana use, which, if you are under 21, is an illegal activity. There is risk associated with reporting this information, but we will keep your information confidential. Because we are not easily linking your name with your substance use behavior and because we are recruiting both marijuana users and non-users, it is extremely unlikely that university authorities or law enforcement could discover that any specific participant used the substances assessed. A waiver has been obtained from the Dean of Students so that Dr. Stewart will not be obligated to report any misconduct as it may relate to marijuana use. Your information will remain confidential unless disclosure is required by law. Examples of two situations are where disclosure is required are: 1) a situation where there is a conversation during the study in which you reveal that you are at serious risk of harming yourself or others and 2) a situation where there is child abuse. No names (only identification (ID) numbers) will be associated with the blood tests and all blood will be analyzed at the same time with other subjects. Samples will be coded so that each collection tube will only be identified with a number so that the technicians or anyone else in the lab will not be able to determine which samples are associated with you.

Initials: _____

All information recorded during the study visits will be coded with an ID number, and this ID number will not be readily connected to you. The only person who will have a written record of a person's name and ID number will be the graduate student and this written information will be kept in a locked cabinet in her office (Gunter Hall Room 2790) and shredded after the study data has been collected. Signed consent forms will be stored in a locked cabinet in your office on campus for a period of three years following the completion of the study, and then destroyed. Additionally, all marijuana use survey responses collected in visit 1 will be obtained by a graduate student who does not know you and is not employed by UNC. In the extremely unlikely situation where the researchers both know you and you disclose marijuana use, the researchers will inform you (if s/he is under 21) that this action is breaking university policy and will provide information and resources to the student about how to quit if you so desire. If you are one of Dr. Stewart's current students, neither your study participation nor drug use information will influence your grade in the course. In this project, will have 3 graduate students working on this project. All data collection will be conducted by researcher who does not know you.

All data files will be protected with passwords and paperwork will be locked in filing cabinets. All research assistants will only have access to ID numbers and will be made fully aware of the importance of protecting confidentiality. All staff will be required to sign a certificate of confidentiality, stating that they will not discuss your marijuana use or inappropriately divulge information to you. All procedures will be closely supervised by Dr. Laura Stewart. Research assistant staff will be trained to provide referrals for drug treatment or the counseling center if you request any information.

Participation

Participation is voluntary. You may decide not to participate in this study, and if you begin participation you may still decide to stop and withdraw at any time. Your decision will be respected and will not result in loss of benefits to which you are otherwise entitled. Having read the above and having had an opportunity to ask any questions, please sign below if you would like to participate in this research. A copy of this form will be given to you to retain for future reference. If you have any concerns about your selection or treatment as a research participant, please contact Nicole Morse, IRB Administrator, Office of Sponsored Programs, 25 Kepner Hall, University of Northern Colorado Greeley, CO 80639; 970-351-1910.

_____ _____

Signature of Investigator Signature of Participant

Date:_____
Witness:_____

Initials: _____