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ABSTRACT

The Impact of Vaping Cannabidiol: A Case Series of Young Adults

By:

Samuel Bullard

The use of e-cigarettes and vape pens has grown in popularity especially among the high school and college aged population. This is a cause for concern because due to its relative novelty not much is known about the long-term impact of vaping. Cannabidiol (CBD) is a compound derived from hemp that is being used in vape pens. Although the oral intake of CBD has been researched, there is still much to be learned about the impact CBD has when vaped. Thus, the purpose of this pilot study is to gather data on cardiovascular, respiratory, and mental health of participants who vape CBD but do not smoke traditional cigarettes. Participants were asked to fill out surveys on their anxiety, depression, past medical history, and alcohol use. Each participant then performed a VO_{2max} test and spirometry test to measure cardiorespiratory function. Data was compared to reference values based on age and gender. Our participants showed very poor cardiorespiratory health and elevated levels of reported anxiety and depression. We speculate that there may be a relationship between vaping CBD and reduced cardiorespiratory function; however, more data needs to be collected to confirm this assumption.

THE IMPACT OF VAPING CANNABIDIOL:

A CASE SERIES OF YOUNG ADULTS

by

Samuel Bullard

A Thesis

Presented in Partial Fulfillment of Requirements for the Degree of

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ABBREVIATIONS

2-AG: 2-arachidonoylglycerol

8-OHdG: 8-hydroxy-2-deoxyguanosine

A2A: Adenosine A2A receptor

AS: Asthmatic smoker

BP: Blood pressure

CRP: C-reactive protein

CBD: Cannabidiol

CB1: Cannabinoid receptor 1

CB2: Cannabinoid receptor 2

CNS: Central nervous system

COPD: Chronic Obstructive Pulmonary Disease

DBP: Diastolic BP

EVALI: E-cigarette or vaping, product use–associated lung injury

EMPs: Endothelial microparticles

FEF25-75%: Forced expiratory flow between 25% and 75% of FVC

FEV1: Forced expiratory volume in one second

FVC: Forced vital capacity

GPR55: G protein-coupled receptor 55

GI: Gastrointestinal

GAD-7: Generalized Anxiety Disorder-7

GRAS: Generally Recognized as Safe

HA: Healthy asthmatics

HNS: Healthy non-smokers

HR: Heart rate

IL-4: Interleukin-4

IL-6: Interleukin-6

AEA: N-arachidonoyl-ethanolamine

NIAAA: National Institute of Alcohol Abuse and Alcoholism

PHQ-9: Patient Health Questionnaire-9

PEFR: Peak expiratory flow rate

PPAR- γ : Peroxisome proliferator-activated receptor gamma

ROS: Reactive oxygen species

SSRIs: Selective serotonin (5-HT) reuptake inhibitors

5-HT_{1A}: Serotonin 1A receptor

SBP: Systolic BP

THC: Tetrahydrocannabinol

TNF- α : Tumor necrosis factor-alpha

FDA: US Food and Drug Administration

CHAPTER I

INTRODUCTION

1.1 Background and Significance

In 2018, the Farm Bill made a distinction between versions of the cannabis sativa plant, calling them hemp and marijuana. Hemp was defined as cannabis sativa that contains less than 0.3% tetrahydrocannabinol (THC) by dry weight and marijuana more than 0.3% THC by dry weight.¹ Cannabidiol (CBD) is one of the key compounds derived from hemp. Unlike THC, CBD has no psychoactive effects besides an anti-anxiety effect at certain dosages.^{2,3} CBD has become a popular product in the US with 64% of American adults familiar with CBD.⁴ Despite the increasing public usage and sale of CBD, the US Food and Drug Administration (FDA) prevents it from being sold or marketed as a dietary supplement due to its status as an approved medication.⁵

CBD has multiple methods of delivery to the body. These include, but are not limited to, the gastrointestinal (GI) tract by oral ingestion, the dermis by topical cream, and the pulmonary system by vaping.⁶ One third of youth reported using vaping for non-nicotine substances in 2015.⁷ From 2017 to 2019, it was shown that the prevalence of vaping has nearly doubled in highschoolers.⁸ Substances that would be vaped alternative to nicotine include both CBD and THC.⁹ The increase in popularity of vaping combined with the recent series of acute lung injury cases associated with vaping demonstrate that vaping is a public health concern.^{8,10}

Little-to-no significant studies have been done that isolate vaping CBD specifically. Both the CBD and the vaping industry are in their infancy, which contributes to an inconsistent quality of both the vaping liquid and CBD oil.¹ There remains a general lack of knowledge related to the long term safety of products used for vaping due to its relative novelty. The literature about vaping focuses on the general impact on lung function.¹¹ Some research suggests that vaping has little impact on measures of lung function measured by spirometry, a commonly used technique to measure lung function in conditions such as Chronic Obstructive Pulmonary Disease (COPD).¹² For example, researchers have tested participants after short term vaping sessions to find that vaping had less of an immediate negative result as compared to smoking traditional cigarettes.^{12,13} However, more sensitive measures of lung health have detected changes in lung tissue such as alterations in the small airway epithelium transcriptome and elevated endothelial microparticles after exposure to vaping that may, over, time cause changes measured by spirometry.^{13,14}

The literature suggests that CBD has little-to-no effect on heart rate (HR) or blood pressure (BP) except in stressful situations.¹⁵⁻¹⁷ CBD is shown to lower HR when taken during exposure to stress.¹⁵⁻¹⁷ Furthermore, CBD seems to reach a maximal level of concentration in the blood after consistent dosage over time.⁶ A method of absorption that bypasses the liver, such as delivery through the lungs would be the most efficient in terms of quickly increasing serum levels; however, this would only speed up the rate to which maximal concentration is reached.⁶

Overall, CBD appears to have anti-inflammatory impacts.¹⁸ This is significant because many of the leading causes of death such as cardiovascular disease are associated with chronic or long-term inflammation.¹⁹ In models of experimentally-induced asthma using rodents, CBD was shown to reduce multiple markers of inflammation that led to a reduction of the asthma-related symptoms.^{20,21} The anti-inflammatory action of CBD occurs through a number of pathways that extend beyond the previously understood endocannabinoid system of cannabinoid receptor 1 (CB1) and cannabinoid receptor 2 (CB2).²²

A review of the literature reveals a dearth of understanding about vaping CBD. Therefore, further research is required to demonstrate the efficacy of vape pens and CBD products to prevent disastrous events such as the 2019 e-cigarette or vaping, product use–associated lung injury (EVALI) outbreak.¹⁰ The cause of the EVALI outbreak has not been clearly determined but was strongly associated with vaping e-liquids that contain vitamin E acetate.¹⁰ Moreover, the ongoing illegal usage of vape pens by the youth across the US compounds this importance.²³ Not only does vaping have the potential to cause harm long-term, but the group most likely to be harmed is the youth of the nation.^{24,25}

The purpose of this study is to gain preliminary data and insight into the impact that vaping CBD has on the body. In this study, we will be using spirometry to measure the lung function, graded exercise testing to measure VO_{2max} , and questionnaires to assess levels of anxiety and depression of individuals who self-report to vape CBD. We expect to see a decreased pulmonary and VO_{2max} function compared to reference rates for age and gender due to the vaping aspect of the study. However, due to the anti-inflammatory, anti-anxiety, and anti-depressant nature of CBD, it could be that participants with higher self-reported

CBD use perform closer to normal compared with reference rates for both cardiorespiratory fitness, anxiety, and depression. To test this hypothesis, we propose the following specific aims:

Aim 1: Determine the impact of vaping CBD on lung and cardiovascular function.

Hypothesis 1: Participants have decreased lung function and lower VO_{2max} compared with reference standards.

Null Hypothesis 1:

Participant values for lung function and VO_{2max} fall within reference ranges or above.

Aim 2: Determine the impact of vaping CBD on anxiety and depression.

Hypothesis 2: Participants have reduced levels of anxiety and depression compared with reference standards.

Null Hypothesis 2: Participant values for anxiety and depression are above reference ranges.

CHAPTER II

REVIEW OF THE LITERATURE

2.1 Vaping & CBD

Having only been legalized by the Farm Bill in 2018, the CBD industry is in its infancy; therefore, it is paramount that we first address the status of commercially produced CBD and its delivery into the body.²⁶ There are currently a lack of established regulations on the CBD industry. In fact, there were several studies that documented CBD products with contents that do not match what is on their label.^{27–29} Instances have varied from simply not containing the amount of CBD advertised to products containing harmful and/or illegal substances.^{11,30,31} The purity of the CBD product should be considered in future research when measuring the physiological impact of vaping CBD with special consideration of the lungs, the site of absorption.

Vape pens work by rapidly heating a liquid into a vapor that can then be inhaled.³² The liquid that is vaporized inside a vape pen is called an e-liquid. The composition of an e-liquid for use in a vape pen is typically made of a diluent, such as propylene glycol or vegetable glycerin, a pharmaceutical/herbal compound, such as CBD or THC, and a flavoring agent such as vanillin and cinnamaldehyde.^{9,33} The e-liquid is turned into an aerosol by a heating coil inside a vape pen. Chen et al. showed that the temperature of a heating coil ranges from 110 – 334°C under conditions of typical vape usage.³² This means that all the ingredients inside an e-liquid need to be heat stable otherwise this process could create unintended, possibly harmful byproducts.³⁴

Many of the ingredients used in vape pens are from the Generally Recognized as Safe (GRAS) list; however, GRAS is a misnomer when applied to substances that are burned and inhaled.³⁵ The original intent of GRAS compounds referred to ingestion through the GI tract not through inhalation.³⁵ Some compounds on the GRAS list may end up being safe to vape, but at this point the research has not demonstrated their safety for that use.³⁶ There are currently compounds which are on the GRAS list and have either been shown to be harmful when inhaled or have negative effects on lung health; these include: diacetyl, vitamin E acetate, cinnamaldehyde, and benzaldehyde.^{37,38} Diacetyl is associated with the development of bronchiolitis obliterans also called “popcorn lung,” which is an irreversible condition that was first discovered in microwave popcorn factories by exposed workers.³⁷ The result of this condition is the scarring and narrowing of the bronchioles in lung tissue that can lead to a progressive decrease in lung performance from tissue damage.³⁹ Vitamin E acetate has been found in the lungs of many patients who have been hospitalized with EVALI and has not been found in lungs without EVALI.^{38,40} Cinnamaldehyde has been shown to increase DNA strand breaks and cell death and to decompose into benzaldehyde at temperatures greater than 60° C.^{32,33,41} Benzaldehyde has been shown to impair with immune function in lung tissue.^{41,42} This occurs through Benzaldehyde interfering with neutrophil action in the lungs in a dose-dependent manner.^{41,42}

These studies show there is a great need for further research and regulation on what should be allowed inside e-liquids. Informing the general population about the potential harm that could come from vaping is important in order to prevent continued EVALI hospitalizations.^{40,43} Additionally, these studies indicate that side-effects for vaping CBD

may not derive from CBD itself but from the many compounds that are included with CBD inside an e-liquid. This should be accounted for in future studies.

2.2 General actions of CBD in the body

The primary system CBD acts on in the body is the endogenous cannabinoid system also called the endocannabinoid system.⁴⁴ The endocannabinoid system functions independently of cannabinoid intake, but was discovered while researchers were studying the psychoactive effect of cannabis and therefore was named “cannabinoid”.⁴⁵ The endocannabinoid system is a group of endogenous lipids and the receptors they bind to that are found throughout the body. To exert their effects, compounds bind to specific receptors and cause a conformational change which sets off a cascade of events within the cell.⁴⁶ CBD binds to many different receptors that impact inflammation, immune function, anxiety, depression, and pain.¹⁸

The two primary endogenous cannabinoid compounds are N-arachidonoyl-ethanolamine (AEA) and 2-arachidonoylglycerol (2-AG).⁴⁷ While both AEA and 2-AG bind to CB1 and CB2, each compound displays differing levels of affinity.⁴⁶ CB1 is located throughout many systems in the body including the central nervous system (CNS), the liver, the reproductive and cardiovascular system, the skeletal muscle, and the GI tract. CB2 is located primarily on immune-related tissue in both the peripheral tissue of the body and in the CNS on the brain microglia which perform functions related to immunity.^{48–50} In the endocannabinoid system, AEA has a high affinity towards CB1 and low affinity for CB2 while 2-AG acts as a full agonist and has moderate-to-low affinity for both CB1 and CB2.⁵¹ The normal flow of the endocannabinoid system is interrupted when compounds

such as THC and CBD are introduced into the body.^{44,52} An example of the interruption of normal endocannabinoid function is the increase in AEA levels when CBD is present.⁵²

The vapor formed from e-liquids can be directly absorbed into systemic circulation, while CBD taken orally must pass through the liver.⁵³ CBD has been shown to undergo a significant first pass effect which occurs when a large percentage of a compound is blocked by the liver.⁵³ Only about 13-19% of CBD ingested makes it past the liver into systemic circulation, but this can be increased if ingested with a high fat meal.⁵³⁻⁵⁵ This low level of absorption highlights a key difference between oral intake of CBD and vaping CBD and has important implications for how CBD impacts the body.

2.3 Vaping and Lung Function

Lung function measured by spirometry is primarily quantified by three key measures: forced expiratory volume in one second (FEV1), forced vital capacity (FVC), and the ratio between FEV1 and FVC which is FEV1/FVC.¹¹ FEV1 represents the amount of air cleared from the large/cartilaginous airways in the pulmonary system and changes in the FEV1/FVC ratio are interpreted as smooth muscle function or structural lung damage.¹¹ FVC is the total amount of air cleared from the lungs during the FEV test.⁵⁶ The effects of vaping on lung function measured through spirometry have been reported in a number of studies; however, human trials have only addressed the acute and sub-acute effects due to the relative novelty of vaping.^{11,12}

There have been several trials that looked at the acute effect of vaping in several different populations including healthy non-smokers (HNS), healthy asthmatics (HA), smokers, and asthmatic smoker (AS). Boulay et al. investigated the impact of a 1 hour vaping session using volunteers that are both HNS (n=20) and HA (n=10).¹² The HNS in

this study were defined as having no diagnosed lung disease and a negative methacholine challenge test. The methacholine challenge test is used as a method to test if a patient has asthmatic symptoms measured by a 20% reduction in FEV1 after exposure to a dose of methacholine.⁵⁷ Researchers found no statistically significant change in FEV1, FVC, or FEV₁/FVC between these two groups.¹² Staudt et al. found a similar lack of impact on spirometry measures after acute exposure in sample of HNS (n=10) that was confirmed by a lack of tobacco metabolites in the urine.¹³

Ferrari et al. compared the impact of vaping nicotine free e-liquids and a traditional cigarette in a sample of smokers (n=10) and non-smokers (n=10).⁵⁸ The two samples were randomized into groups so that there were five smokers and five non-smokers in each group. There was no set dosage of the amount of vape or smoke the participants were exposed to because the authors wanted to measure the impact of an ad libitum model as this more accurately mirrors the actual use of these products in society.⁵⁸ After five minutes of ad libitum vaping, Ferrari et al. measured a small and statistically significant decrease in both FEV1 and forced expiratory flow at 25% in the group of smokers after using the e-cigarette but saw no change in FEV1, FVC, or FEV₁/FVC for the non-smokers who vaped.⁵⁸

Lappas et al. investigated changes in lung function caused by vaping in a population of smokers with asthma and smokers without asthma.⁵⁹ In this study design, the baseline was measured in a controlled vaping session that used disabled vape pens. This was followed by baseline spirometry measurements. The participants were then exposed to five minutes of vaping using activated vape pens before they once again took spirometry measures. They found that smokers with asthma had significantly reduced spirometry

measures in every category except for FVC.⁵⁹ This finding suggest that smokers who have asthma should attempt alternative cigarette replacement strategies and demonstrates that vaping is not a harmless replacement of traditional cigarettes.⁵⁹ Further research into the effect of vaping in populations with pulmonary diseases should be conducted in order to provide guidelines for the warnings that should be placed on vaping products.

Overall, a review of the acute effect of vaping in a healthy, non-smoker population as measured by FEV1, FVC, or FEV1/FVC is mixed and suggests little effect compared to classic cigarette usage which causes almost immediate bronchoconstriction.^{12,13} However, as pointed out by Gotts et al., the damage caused to lung tissue by chronic smoking can only be detected by spirometry after a significant amount of time has passed, even though there are other methods of measurement that can detect the disruption of homeostasis in the lungs much sooner.^{11,60} In summary, spirometry was not able to detect significant changes in lung function after an acute exposure to vaping; however, the lack of significance detected could be due to a number of factors including, small sample size, small dosage, and an insensitive lung function test.

Other studies were successful in detecting the impact of vaping on lung function after acute exposure when using different methods of measurement.¹³ Gordon et al. demonstrated that endothelial microparticles (EMPs) are a measure of early damage to lung tissue in smokers.⁶¹ This same measure was used by Staudt et al. in their investigation of the acute effects of vaping. They found slightly elevated EMPs in the group that used e-cigarettes without nicotine and significantly elevated EMPs in e-cigarettes with nicotine.¹³ Staudt et al. also measured the small airway epithelium transcriptome and alveolar macrophage transcriptome before and after vaping. Regardless of whether the participants

were exposed to nicotine or not there was a significant number of genes that were upregulated and down regulated. A key difference that was noted between the two groups was that many of the altered genes in the group that vaped nicotine were associated with p-53 signaling, a commonly recognized tumor suppressor gene.^{13,14} All the previously mentioned effects were found in participants who, when measured by spirometry, did not test significantly different from the control despite a clear impact to the lung tissue being shown by different more sensitive measures.

2.4 The Hemodynamic Effects of CBD

To our knowledge, no studies have examined the impact of vaping CBD on VO_{2max} , a measure of cardiovascular fitness. Electronic vaping and CBD seem to have opposing effects on the cardiovascular system.⁶²⁻⁶⁴ Electronic vaping, even without nicotine, is not benign even though it appears to have less of an impact on the pulmonary system than cigarette smoke or vaping nicotine.⁶⁵ Negative impact on the pulmonary and cardiovascular system should lead to a decrease in VO_{2max} .⁶⁶

The impact of CBD on the cardiovascular system seems to be anti-inflammatory and adaptogenic, which includes a decrease of BP and HR during exercise.^{64,67} Adaptogenic is defined by Panossian and Wikman as herbal preparations that increased attention and endurance in fatigue, and reduced stress-induced impairments and disorders related to the neuro-endocrine and immune systems.^{68,69} It could be that CBD is able to mitigate the impact vaping has on cardiovascular measures, but this question has not been answered by any peer reviewed study.

2.5 Acute Dosage of CBD and Cardiovascular Outcomes

There is currently mixed evidence on the acute impact of CBD on the cardiovascular system. Some evidence shows that when using acute doses on *in vivo* studies there is no effect on variables like HR and BP.^{15,16,70} Hallak et al. looked at the interaction between CBD and ketamine in healthy human subjects and measured HR and blood pressure throughout the study.¹⁶ Martin-Santos et al. investigated the effects of THC and CBD in healthy volunteers.¹⁵ Both groups found that an acute dose of 600 mg of CBD had no impact on HR, systolic BP (SBP), or diastolic BP (DBP) in healthy participants.^{15,16} Furthermore, Zuardi et al. looked at the effect of CBD in a stressful environment caused by public speaking.⁷¹ They found no acute impact of CBD on HR or BP.⁷¹ While all three of these human trials show no impact of CBD on HR and BP, Jadoon et al. showed an acute decrease in BP and increase in HR in both exercise and cold induced stress after using 600 mg of CBD.⁶⁷

Resstel et al. studied male Wistar rats under stress in a contextual conditioned fear paradigm that used randomized foot shocks.⁷² In this study, rats were given either placebo, diazepam, or CBD and were then further separated into preconditioned or unconditioned groups.⁷² They found a dosage of 10 mg/kg CBD before shock stress exposure reduced HR and mean arterial pressure in the conditioned animals.⁷² These findings were reported again by Resstel et al. in 2009 using a rat restraint stress model and a CBD dose of 1, 10, or 20 mg/kg.⁷³ In this follow up research, Resstel et al. gave WAY100635, an antagonist to the serotonin receptor 5-HT_{1A}, to a subset of the CBD group and found that the HR and BP of these rats mirrored the control.⁷³ The authors concluded that 5-HT_{1A} is a possible mechanism through which CBD inhibited the cardiovascular effects of stress.⁷³ This agrees

with previous research into the 5-HT_{1A} receptor, which has shown to be expressed in regions of the brain that process stress.^{73–75}

Literature suggests that CBD may affect HR and BP in participants but only in certain stressful conditions. For example, Sultan et al. studied the impact of CBD during exercise over time.⁷⁶ They found a reduction in SBP during exercise on day one and seven while participants were taking CBD for seven days at 600 mg/day.⁷⁶ While there was a change on both testing days, the reduction in SBP during exercise on day 1 was more potent and lasted longer than on day 7.⁷⁶ The reduced change in SBP suggests that the body developed tolerance to CBD's positive cardiovascular effects that seem to occur under stress.⁷⁶ A longer term CBD study further exemplifies that CBD may not have a direct connection to improving cardiovascular health as measures by HR or BP. In a study by Consroe et al., participants received CBD at a dosage of 10 mg/kg/day for 6 weeks in a double-blind crossover design and found no change to HR or BP at the end of the 6 weeks.¹⁷ The average body weight in this study was 67.6 +/- 16.9 kg. This means the participants were given 676 +/- 169 mg CBD/day which roughly equates to the common 600 mg dose that has been used in previously mentioned studies but found no change to HR or BP.^{15,16,64}

Due to the relative novelty of CBD legal status, there has not been enough time for any major long-term studies to be conducted. The reduction in HR and BP in stressful situations has been demonstrated in mice,^{72,73} but also in humans.^{64,67} While the study by Zuardi et al. may seem to contradict this conclusion, it could be that the stress caused by public speaking was not significant enough to differentiate the HR and BP reducing effect.⁷¹ In the absence of stress, CBD does not seem to influence HR or BP in either acute and chronic dosage.^{15–17} This suggests that CBD may have application in helping the body

to adapt to stress induced by both physical and psychological stressors; however, the long-term benefit of a reduction in HR and BP only during stress needs to be further researched.

2.6 CBD Dosage in Emotional and Mental Function

According to Corroon and Phillips, the top three reasons for using CBD is pain, anxiety, and depression.⁷⁷ CBD does interact with receptors associated with mood, anxiety, and depression.^{18,78} An important question to consider is: are people who vape CBD getting the right dose to use the anxiolytic or anti-anxiety effect of CBD? The ad libitum use of vape pens as well the varying dosage of CBD in the e-liquids make this difficult to determine; however, the literature suggests that there is an ideal dosage range of CBD for its anxiolytic effect.^{2,3}

In the study examining the dosage of CBD and public speaking by Zuardi et al. mentioned previously, participants were randomized into 5 different groups, three of the groups were given oral CBD through pills at dosages of 100 mg, 300 mg, and 900 mg. The results of the study showed that the 100 mg and 900 mg groups were more anxious, as measured by the visual analog mood scale, than the 300 mg group during public speaking.² Linares et al. found similar results to Zuardi et al. They investigated three doses of 150, 300 and 600 mg and found 300 mg to be the most effective dose.³ There are also several other studies that used single doses with varying effects.^{15,79,80} Crippa et al. tested a single, oral dose of 400 mg and found significantly reduced anxiety; however, both Bhattacharyya et al. and Martin-Santos et al. tested the oral dosage of 600 mg with different results.^{15,80} Bhattacharyya et al. found 600 mg to be effective at reducing anxiety while Martin-Santos et al. did not find significance in the reduction of anxiety compared to control.^{15,80} A clear limitation to these studies is that they reported their results as the mass of the dosage and

not by mg/kg/day as the variation in the participant weight could be a possible explanation for the variation in findings.

Epidiolex, the only FDA approved CBD medication, is pure CBD and has a starting dosage of 5 mg/kg/day with a maximum 10 mg /kg/day.⁸¹ Epidiolex was approved primarily by the FDA as a treatment for Lennox-Gastaut syndrome or Dravet syndrome, both of which are types of childhood epilepsy.^{2,3,81} Epidiolex as a treatment for anxiety would be an off label usage; however, for an individual between 60 and 80 kg the 5-10 mg/kg/day dosage would fall inside the 300-400 mg range that seems to be ideal for an anxiolytic effect.^{2,3,81}

2.7 CBD and Inflammation

Inflammation is the body's response to stimuli that it considers harmful, and results in the initiation of a healing response that includes a mobilization of the immune system to return the injured tissue to homeostasis.⁸² Depending on the context, inflammation can be helpful or harmful. In general, acute inflammation is typically helpful to the body while chronic inflammation is harmful.⁸³ Short-term inflammation leads to the healing and resolution of the injury to the body.⁸² Chronic inflammation plays a significant role in many of the leading causes of death worldwide.¹⁹ Diseases that are associated with chronic inflammation include cardiovascular diseases, atherosclerosis, type 2 diabetes, rheumatoid arthritis, and cancer.^{82,84} During inflammation, proteins called cytokines are released to either increase and continue the inflammatory response or reduce and resolve the inflammatory response in the body.⁸⁴ These signaling proteins are released by immune cells in response to different signals.⁸⁵ Biomarkers that are used to measure inflammation

include but are not limited to interleukin-6 (IL)-6, tumor necrosis factor-alpha (TNF- α), and C-reactive protein (CRP).

Oxidative stress leads to the production of reactive oxygen species (ROS) which can activate the inflammatory response.⁸⁶ One of the measures of oxidative stress in the body is 8-hydroxy-2-deoxyguanosine (8-OHdG), which is a product of the repair process to damaged guanine, a component of DNA.⁸⁶ By mitigating oxidative stress they can help limit the long term activation of inflammation through oxidative stress that could contribute to chronic inflammation. This is where antioxidants play a role in inflammation. Antioxidants enter the body through foods containing vitamin C, vitamin E, and polyphenols but can also come from herbal derived compounds like CBD.^{18,86,87}

In 2015, Vuolo et al. found changes in serum cytokine levels in male adult Wistar rats with experimentally-induced asthma.²¹ The rats that had both CBD and asthma experienced a significant reduction in TNF- α , IL-6, and other inflammatory markers. In 2019, Vuolo et al. used a similar model in 147 Balb/c mice.²⁰ While TNF- α and IL-6 were not measured in this study, similar markers of inflammation, interleukin-4 (IL-4) (5 mg/kg CBD) and IL-5 (5 mg/kg and 10 mg/kg CBD) experienced a statistically significant reduction.²⁰ These studies show that CBD can play a positive role in mitigating unwanted inflammatory responses such as an asthma attack.^{20,21}

CBD demonstrates both direct and indirect antioxidant capacity.¹⁸ CBD directly affects oxidative stress in the body through interrupting free radical chain reactions.⁸⁷ This action has been attributed to the phenol ring in its chemical structure.⁸⁷ In addition, CBD prevents the formation of superoxide radicals⁸⁸ and reduces ROS.⁸⁹ When compared to α -tocopherol, CBD has higher ROS scavenging capacity but less oxidative stability.⁹⁰ This

is significant when considering the shelf life of CBD oils. It should be noted that while CBD can behave as an antioxidant directly, the most significant antioxidant effects that come from CBD are due to its indirect effects through its interaction with different receptors.¹⁸

CBD has been shown to produce both anti-inflammatory and pro-inflammatory responses when binding to different receptors throughout the body.^{22,91} CBD has a proinflammatory response through CB1 and an anti-inflammatory response through the CB2 receptor, the Adenosine A2A receptor (A2A), the G protein-coupled receptor 55 (GPR55), and the serotonin 1A receptor (5-HT_{1A}).^{22,91} There is still disagreement in the literature over whether CBD has the ability to bind to CB1.^{22,91} As pointed out in a review by Burstein, CBD has a significantly different conformation than THC, which is known to bind at CB1. Due to its different conformation, it should not be able to bind to CB1.²² However, other reviews have found that CBD has a mean pooled affinity of $K_i = 3245 \pm 803$ nM which shows weak activation of CB1. A possible explanation is that CBD may not directly bind to CB1 but still has a weak indirect activation of CB1.⁹¹ When CBD activates CB1 it creates a proinflammatory response.⁹² This proinflammatory response occurs through the CB1 receptors found on macrophages that release TNF- α , a biomarker that is responsible for inflammatory signaling and triggering cell death, and increased measurements of the levels of ROS^{92,93}

CBD may also act on several anti-inflammatory receptors, including CB2 for which it has a weak affinity ($K_i = 22.7 \pm 3.9$ nM). Binding of CB2 has shown to reduce the levels of TNF- α in tissue and in serum.⁹⁴ Indeed, a study by Castillo et al. demonstrated a reduction in IL-6 and TNF- α expression in hypoxic mouse brain tissue when treated with

CBD.⁹⁵ The authors put forth that the mechanism of action occurred through the CB2 and A2A receptors.⁹⁵ When acting through the A2A receptor, CBD appears to have anti-inflammatory and immunosuppressive effects.⁹⁶ Interestingly, this was shown to improve outcome in models of Alzheimer's disease in rodents.⁹⁶ Other agonistic roles of CBD include its activation on the serotonin receptor 5-HT_{1A} which protects cell membranes from peroxidation and on peroxisome proliferator-activated receptor gamma (PPAR- γ) which controls the behavior of macrophages.⁹⁷⁻⁹⁹ It should be noted that PPAR- γ activation also plays a role in modifying the behavior of macrophages to act in an anti-inflammatory capacity.⁹⁷ CBD is an antagonist of the receptor GPR55.¹⁰⁰ When 2-AG, an endogenous cannabinoid, binds to GPR55 under normal conditions, it activate a pro-inflammatory response.¹⁰¹ This was made clear in GPR55 knockout mice that showed elevated levels of anti-inflammatory interleukins IL-4, IL-10.¹⁰²

CHAPTER III

METHODOLOGY

3.1 Study Design

This pilot study was designed to collect data and analyze the effects of vaping on several biomarkers. Eligible and consenting volunteers completed multiple questionnaires, performed lung and cardiovascular health tests, and provided a blood sample.

3.2 Participant Recruitment

The subjects that were recruited were between the ages of 18 and 44, as verified by a photo ID, who self-reported vaping CBD within the last 30 days without traditional cigarette usage. Subjects were recruited using flyers posted on Georgia State's Campus, at local vape shops and at CBD health stores.

3.3 Qualtrics Survey

Data about each participant was collected through a short Qualtrics questionnaire (see Appendix A). This survey took approximately 20-25 minutes. The purpose of the survey was to record demographic information, level of CBD oil usage, delivery methods of CBD (oral, vaped, topical), the frequency of THC usage, and the usage of other substance that could influence results. The Penn State Electronic Cigarette Dependence Index was used as part of the Qualtrics survey to assess the frequency and dependence of CBD usage.

The survey was originally designed to assess these variables related to electronic cigarettes that contain nicotine.¹⁰³ It has been adapted to assess the same variables but for CBD usage by changing mention of “nicotine” to “CBD oil.” Questions from The National Institute of Alcohol Abuse and Alcoholism (NIAAA) were used as part of the Qualtrics survey to assess alcohol usage.

3.4 Patient Health Questionnaire-9 (PHQ-9)

The PHQ-9 was used to screen for depression in participants (see Appendix B). The PHQ-9 has been validated as a reliable measure for depression severity.^{104(p9)} Scores for depression from this survey range from one through four. The higher the score the more severe the depression.

3.5 Generalized Anxiety Disorder-7 (GAD-7)

The GAD-7 was used to assess anxiety levels in participants (see Appendix C). Like the PHQ-9 it also gives scores that range from one through four with a higher number meaning increased levels of anxiety. The PHQ-9 and GAD-7 surveys were used to determine what population characteristics are more likely to be associated with CBD usage.

3.6 Graded Exercise Testing

After providing informed consent and being cleared for the exercise portion of the study, subjects completed a graded exercise test inside the Respiratory Therapy Lab PSC457. Subjects were cleared if they did not exhibit or report any of the following: bone spurs, arthritis, joint disorders that impact cycling ability, pregnancy, medications such as Azithromycin, and other diseases that could increase the likelihood of a cardiac event. Weight without shoes was recorded for each participant. Subjects were put on the metabolic cart equipment (Quark CPET, Cosmed: Rome, Italy) and were asked to sit for 5

min while the air temperatures and gas composition reached equilibrium in the room and machine. We recorded minute ventilation and tidal volume at rest. Subjects were asked to continue cycling as long as they were able. The initial resistance was set at 50 Watts and increased by 25 Watts every 2 min. Throughout the test, a metabolic cart was used to record gas exchange variables. We defined VO_{2max} as the highest 15-sec average during testing.

3.7 Spirometry Testing

To test lung function, subjects were given a standard spirometer (Spiro Air, Medisoft: Sorinnes, Belgium). Participants took a deep breath and forcefully exhaled as long as possible to measure the FVC of the lungs. The FEV_1 was measured during this forced breath as the amount of air the subject exhaled during the first second. Participants also performed a 12-sec maximum ventilation test to see how much air they can inhale and exhale deeply during a 12-sec period.

3.8 Statistical Analysis

After gathering all the above data from each participant, researchers compiled, organized, and standardized the measures for comparison. Reference values were used to create a list of standard measures for each test in a general population that does not specifically vape CBD. Each of the biomarkers was collected so that it could be compared to normal ranges to see if there were any abnormalities in participants that vape CBD. The data analysis that was used in this pilot study was to detect trends in the data using descriptive statistics. Linear regression was used to characterize the association between predictor variables (sex, age, education, race/ethnicity, depression, and anxiety) and the level of CBD usage. In this analysis we controlled for alcohol use, THC use, nicotine use,

administration of CBD orally or topically, and the use of other substances that were control variables in the study.

3.9 Ethical Considerations

All participants were informed of the purpose of the study and were told of the voluntary nature of their participation and that they were free to withdraw from the study at any time. Participants received a \$20.00 gift card, which was given at the completion of individual data collection, as compensation for participating in this study. All participants were informed of the confidentiality of their personal information. A code was used instead of names on all study records. All information provided was kept in locked security cabinets and password protected computers. Participants were provided with a copy of the informed consent document (see Appendix D) as well as the Georgia State IRB phone number and email address to contact if they had any questions.

CHAPTER IV

RESULTS

4.1 Participant Demographics

The data set for the study only contains two participants, one female (participant A) and one male (participant B). Both participants reported regular usage of vaping CBD but with different rates of usage. Participant A used CBD daily while participant B used CBD monthly (Table 1). In our sample, participant A reported using only CBD whereas participant B reported using both CBD and THC. CBD dependence was measured using an adapted Penn State Electronic Cigarette Dependence Index, which gives values from 0 – 13+ that are then used to categorize the level of dependence. Participant A had a score of 1 and participant B had a score of 6. These values can be interpreted as no dependence to low level of dependence on CBD usage (Table 1).

4.2 NIAAA Questionnaire

Participant alcohol usage history was assessed using the National Institute of Alcohol Abuse and Alcoholism questionnaire. As shown in Table 1, both participants report regular usage of alcohol and have a history of binge drinking although it only occurred during 1 or 2 days in the past year.

Binge drinking is defined as 4-5 drinks in under 2 hours.^{105,106} Both participants reported that the maximum drinks consumed in 24 hours was 8-11 drinks (Table 1); however, the amount reported that is usually consumed during a sitting and how often they drink in a year is different. As indicated in Table 1, participant A reported drinking alcohol 3-11 times in the past 12 months but consuming 5-6 drinks at a time while participant B reported drinking alcohol weekly, but typically consuming 2 drinks at a time.

4.3 Participant Anxiety and Depression

A generalized anxiety disorder score was obtained for all participants and the mean score was 17 (5.66) (Table 1). A score above 10 can indicate generalized anxiety disorder.¹⁰⁷ This indicates that the participants in the study experienced a relatively elevated level of anxiety. Participant A had a score of 21 while participant B had a score of 13. On the patient health questionnaire, participant B scored in the moderate depression range (13) while participant A scored in the moderate severe depression range (17).

Table 1. CBD use among participants

	Participant A	Participant B	CBD participants N=2 (100%)
CBD vaping patterns			
Vaping CBD oil only	1 (50%)	0	1 (50%)
Vaping CBD + THC	0	1 (50%)	1 (50%)
Currently ingest CBD			
Yes	1 (50%)	1 (50%)	2 (100%)
No	0	0	0 (0%)
Frequency of ingesting CBD products			
Daily	1 (50%)	0	1 (50%)
Monthly	0	1 (50%)	1 (50%)
CBD vaping cessation is difficult			
Yes	1 (50%)	0	1 (50%)
No	0	1 (50%)	1 (50%)

CBD dependence index score	1	6	3.50 (3.53)
Alcohol use past 12 months (Q12)			
Every day	0	0	0
5-6 times a week	0	0	0
3 to 4 times a week	0	0	0
Twice a week	0	0	0
Once a week	0	1 (50%)	1 (50%)
2-3 times a month	0	0	0
Once a month	0	0	0
3-11 times in the past year	1 (50%)	0	1 (50%)
Most drinks consumed in a 24-hour period during lifetime (Q13)			
36 drinks or more	0	0	0
24 to 35 drinks	0	0	0
18 to 23 drinks	0	0	0
12 to 17 drinks	0	0	0
8 to 11 drinks	1 (50%)	1 (50%)	2 (100%)
5 to 7 drinks	0	0	0
4 drinks	0	0	0
3 drinks	0	0	0
2 drinks	0	0	0
1 drink	0	0	0
Typical alcohol consumption in one sitting over the last 12 months (Q15)			
25 or more drinks			
19 to 24 drinks	0	0	0
16 to 18 drinks	0	0	0
12 to 15 drinks	0	0	0
9 to 11 drinks	0	0	0
7 to 8 drinks	0	0	0
5 to 6 drinks	0	0	0
3 to 4 drinks	1 (50%)	0	1 (50%)
2 drinks	0	0	0
1 drink	0	1 (50%)	1 (50%)
	0	0	0
Number of binge drinking event during the last year (Q18)			
Every day	0	0	0
5 to 6 days a week	0	0	0
3 to 4 days a week	0	0	0
two days a week	0	0	0
one day a week	0	0	0
2 to 3 days a month	0	0	0
one day a month	0	0	0
3 to 11 days in the past year	0	0	0
1 or 2 days in the past year	1 (50%)	1 (50%)	2 (100%)

Generalized Anxiety Disorder Score, Range 0-21	21	13	17 (5.66)
Patient Health Questionnaire (PHQ-9) depression score, range 1-27	17	13	15 (2.83)

4.4 Spirometry Measures

FEV₁ is defined as the amount of air that is forcibly expelled from the lungs in the first second of a spirometry test, and FVC is the total volume of air pushed out of the lungs in one breath.⁵⁶ For participant A the FEV₁ (108%) and FVC (153%) were above the predicted values, indicating adequate function of large airway structures, while their FEV₁/FVC (63%), and FEF25-75% (86%) were below predicted values (Table 2).⁵⁶ The reduced forced expiratory flow between 25% and 75% of FVC (FEF25-75%) indicates possible dysfunction of the small airway.⁵⁶ For participant B, only the FVC (113%) was within normal ranges whereas FEV₁ (58%) was at reduced levels as well as FEV₁/FVC (43%) and FEF25-75% (49%) (Table 2). The reduced FEV₁ value could indicate an obstructive condition affecting large airway structures in addition to also having reduced small airway function similar to participant A.⁵⁶ The peak expiratory flow rate (PEFR) measures the maximum air rate being pushed from the lungs. This was the most reduced value in both participant A (54%) and participant B (24%) (Table 2).

Table 2. Pulmonary function test results for CBD study participants (n=2).

	Actual Value	Predicted Value	Percentage (Actual/Predicted)
Participant A			
FEV ₁ (L/min)	3.12	2.9	108%
FVC (L/min)	4.95	3.23	153%
FEV ₁ /FVC (%)	63	90	---
FEF25-75% (L/s)	3.1	3.59	86%
PEFR (L/min)	3.51	6.47	54%
Participant B			
FEV ₁ (L/min)	2.38	4.08	58%

FVC (L/min)	5.48	4.84	113%
FEV ₁ /FVC	43	85	---
FEF _{25-75%} (L/s)	2.12	4.36	49%
PEFR (L/min)	2.38	10.1	24%

4.5 Participant Cardiorespiratory Fitness

Both results on the VO_{2max} test revealed that the participants were in the “very poor” category for cardiorespiratory fitness according to ACSM’s guidelines for exercise testing and prescription.^{108,109} Participant A had a VO_{2max} of 23.9 ml/kg/min and participant B had a VO_{2max} of 28.8 ml/kg/min which are far below a normal value for age and gender (Table 3). To compare, a VO_{2max} of 23.9 ml/kg/min is in the 50th percentile for someone who is 50-59, and a VO_{2max} of 28.8 ml/kg/min is in the 50th percentile for someone who is age 60-69.¹⁰⁹ These values indicate that the cardiorespiratory fitness of our sample is substantially decreased compared the reference values for their age and gender.

Table 3. VO_{2max} test results for CBD study participants (n=2).

	VO _{2max} (ml/kg/min)	Percentile Ranking
Participant A	23.9	10%
Participant B	28.8	<5%

CHAPTER V

DISCUSSION

5.1 Participant Recruiting

Originally, the study intended to recruit approximately 10 participants to act as a pilot study to assess the characteristics of different biomarkers related to individuals who vape CBD. However, participant recruitment was challenging due to several factors. The COVID-19 pandemic vastly limited participant interest and participant ease of access to the testing environment. Our primary participant population was college students and due to the COVID-19 pandemic, college students were no longer on campus due to social distancing. Another reason was the initial inclusion criteria only included individuals who solely vaped CBD. Through the recruitment process, we were reminded that most people who vape CBD also vape other substances. Additionally, these other substances may be of questionable legality, which may make individuals hesitant to participate in the research study due to concerns of their identity being revealed.¹¹⁰

5.2 CBD Dosage, Anxiety, and Depression

The participants in the study reported using CBD in drastically different amounts: one monthly and one daily. Furthermore, the nature of vaping in general is not one of a highly precise dosage but of usage whenever the user desires. The way vaping functions makes it difficult to track the exact amount of CBD inhaled for the typical user.

Because of these inconsistencies, trying to predict the outcomes, especially related to anxiety, based on dosage is quite difficult. CBD seems to induce an inverted U shape dose response curve related to stress reduction.^{2,3} At high dosages of CBD, the vanilloid receptor TRPV1 is activated which seems to increase anxiety based on current research.^{2,111} There does seem to be a maximal saturation of CBD in the body with prolonged usage at a consistent dosage so effects of CBD may become leveled out and consistent; however, this has not been tested.⁶

The participants reported elevated levels of anxiety. Further research is needed to distinguish whether high levels of anxiety are common in a population who vapes CBD or in a population who vapes in general. Currently, CBD is advertised as an anti-anxiety substance. However, one concern of using CBD for anti-anxiety is the previously mentioned inverted U-shaped dose response curve related to anxiety under stress.^{2,3} Though CBD activates the cellular mechanism of the 5-HT_{1A} receptor known to be involved in its anti-anxiety effects, the lack of dosage precision when vaping CBD could lead to it being ineffective at reducing anxiety.^{2,3} For instance, if someone is going through a period of elevated stress and decides to increase their usage of CBD through increased vaping to counteract their stress, it could become ineffective or possibly make their stress levels worse than before. It seems plausible that people who are using CBD to manage their stress levels could become dependent, but our participants reported very low levels of emotional dependence on CBD (Table 1).

In this study, participant depression scores ranged from moderate (13) to moderately severe (17). CBD seems to help alleviate symptoms of depression through the activation of 5-HT_{1A} receptors, which has a similar mechanism of action to selective serotonin (5-

HT) reuptake inhibitors (SSRIs).^{112,113} It could be that participant depression scores would have been higher if not for their usage of CBD; however, more research needs to be done to determine the effective dosage and duration of use of CBD to affect symptoms of depression.

5.3 Participant Cardiorespiratory Health

Before discussing cardiorespiratory health, it is important to understand the confounding variables related to vaping CBD. Our sample includes a participant who reported vaping THC. It has been shown that THC is associated with the EVALI outbreak in 2019, which suggests it is not benign.¹¹⁴ Furthermore, the e-liquids used in vaping are unregulated and contain a variety of compounds, such as GRAS flavors which have a negative impact on lung and cardiovascular health when vaped.^{37,38} Because of the lack of regulation of e-liquids, products claiming to contain only CBD may not include an accurate amount of CBD as labeled and may contain other substances with unknown implications on the lung health such as pesticides, unadvertised THC, and synthetic cannabinoids that are not included on the label.^{27,115–117} These impurities could be some of the contributing factors to the tissue inflammation and damage found in the lungs of those who regularly vape.

In our study, both participants showed reduced lung function as measured by spirometry. Based on the results of the FEF25-75%, both participants show results similar to those who have damage to the small airways in the lungs.⁵⁶ However, this cannot be confirmed at this time. Furthermore, even if damage to the small airways were to be confirmed in our participants, it would be unknown whether it was directly related to the use of CBD, or another substance found in the e-liquid used for vaping. A study by Staudt et

al. has shown evidence that after only 10 “puffs” of an e-liquid containing nicotine in a population who has never smoked or vaped lung tissue is impacted at a cellular level.¹³ The most dramatic changes were statistically significant increases in plasma endothelial microparticles, which are biomarkers of early lung tissue damage, as well as alterations to the transcriptome of the small airway epithelium and alveolar macrophage.^{13,61} The changes in lung tissue after acute exposure offer a possible explanation for the mechanism through which chronic vaping could cause harm as well as provide contradictory evidence against the idea that vaping is a benign practice.

Based on the reduced function of lung tissue measured by spirometry in our sample, it should not be a surprise that the participants in our study performed below the 50th percentile during a $\text{VO}_{2\text{max}}$ test (Table 3). However, the participants in this study were not simply below average. Participant A in this study was measured at the 10th percentile and participant B was below the 5th percentile for their age and gender. This demonstrates significantly reduced cardiorespiratory fitness which is suggestive of poor performance from both the lungs and cardiovascular system in terms of effectively transporting oxygen to the rest of the body. While there is not yet research looking at vaping and $\text{VO}_{2\text{max}}$, Caporale et al. has shown that vaping a nicotine free e-liquid causes acute endothelial dysfunction and impaired microvascular function in a sample of healthy, nonsmoker individuals.⁶² These findings suggest that the low $\text{VO}_{2\text{max}}$ observed in our participants is likely a result of both respiratory and cardiovascular impairment.

CHAPTER VI

CONCLUSION

E-cigarettes have become very popular with 3.6 million middle school and high school aged users.^{23,118} As regulators and lawmakers attempt to catch up with this sudden increase in popularity there is a surprising lack of research covering the possible effects and implications of sustained usage of e-cigarettes and more specifically the use of e-cigarettes containing CBD. The EVALI outbreak in 2019 is a demonstration that vaping is not benign and that simply because a compound is recognized as safe to consume does not mean it is safe to vape.³⁸ Though CBD is viewed as generally beneficial and “healthy” due to current marketing to the general population, it has been well documented that those products are often mislabeled and may contain contaminants.^{27,115–117} The participants in the study showed concerning results regarding their cardiorespiratory fitness and mental health but more research needs to be done to determine if this is representative of the general population who vapes CBD and if CBD is contributing to or mitigating these outcomes.

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APPENDICES

A. QUALTRICS SURVEY

Demographic Information

1. Sex
2. Age (in years)
3. Year in college
 - a. Freshman
 - b. Sophomore
 - c. Junior
 - d. Senior
 - e. No college
 - f. Grad student
4. Race/ethnicity Classification Questions
 1. In the past 30 days, which of these products have you used?
 - a. Vaping CBD oil only
 - b. Vaping THC oil only
 - c. Vaping both CBD and THC oil
 2. Do you currently vape nicotine or use electronic cigarettes that contain any nicotine?
 - a. Yes
 - b. No
 3. Do you currently ingest CBD orally?
 - a. Yes
 - b. No
 4. If so, how often do you ingest CBD orally?
 - a. Daily
 - b. Weekly
 - c. Monthly
 - d. Rarely
 5. Do you currently apply CBD topically?
 - a. Yes
 - b. No

6. If so, how often do you apply CBD topically?
 - a. Daily
 - b. Weekly
 - c. Monthly
 - d. Rarely

Penn State [Electronic] Cigarette Dependence Index

For this survey, we will be referring to your electronic cigarette filled with CBD oil only. Do you currently use an electronic cigarette or electronic vaping device filled with CBD? Yes (Proceed to survey)/ No

1. How many cigarettes [times] per day do you usually smoke [use your CBD electronic cigarette]?
(assume that one "Time" consists of around 15 puffs or lasts around 10 minutes)
 - a. (Scoring: 0-4 times/day= 0, 5-9 times=1, 10-14=2, 15-19=3, 20-29=4, 30+=5)
2. On days that you can smoke [use your CBD electronic cigarette] freely, how soon after you wake up do you smoke your first cigarette [first use your electronic cigarette]?
 - a. (Scoring: 0-5 min=5, 6-15=4, 16-30=3, 31-60=2, 61-120 1, 121+=0)
3. Do you sometimes awaken at night to have a cigarette [to use your CBD electronic cigarette]? a. Yes (1)
b. No (0)
4. If yes, how many nights per week do you typically awaken to smoke [use your CBD electronic cigarette]?
 - a. (Scoring: 0-1 nights=0, 2-3 nights=1, 4+ nights=2)
5. Do you smoke [use a CBD electronic cigarette] now because it is really hard to quit? a. Yes (1)
b. No (0)
6. Do you ever have strong cravings to smoke [use a CBD electronic cigarette]? a. Yes (1)
b. No (0)
7. Over the past week, how strong have the urges to smoke [use your CBD electronic cigarette] been?
 - a. (Scoring: None/slight=0, Moderate/Strong=1, Very strong/extremely strong=2)
8. Is it hard to keep from smoking [using a CBD electronic cigarette] in places where you are not supposed to?
 - a. Yes (1)
 - b. No (0)

When you haven't used [your CBD electronic cigarette] for a while or when you tried to stop smoking your electronic cigarette....

9. Did you feel more irritable because you couldn't smoke [use an electronic cigarette]? a. Yes (1)
b. No (0)
10. Did you feel nervous, restless, or anxious because you couldn't smoke [use an electronic cigarette]?
 - a. Yes (1)
 - b. No (0)

Total scoring:

0-3=not dependent

4-8=low dependence

9-12= medium dependence

13+= high dependence

The survey can interchange electronic cigarettes with CBD to:

1. Electronic Cigarettes without CBD/THC
2. Electronic Cigarettes with THC

Alcohol Use Questionnaire (NIAAA) <https://www.niaaa.nih.gov/research/guidelines-and-resources/recommended-alcohol-questions>

Question 1 - (asks about frequency of past 12-month drinking)

1. During the last 12 months, how often did you usually have any kind of drink containing alcohol? By a drink we mean half an ounce of absolute alcohol (e.g. a 12 ounce can or glass of beer or cooler, a 5 ounce glass of wine, or a drink containing 1 shot of liquor). Choose only one.
 - a. Every day
 - b. 5 to 6 times a week
 - c. 3 to 4 times a week
 - d. twice a week
 - e. once a week
 - f. 2 to 3 times a month
 - g. once a month
 - h. 3 to 11 times in the past year
 - i. 1 or 2 times in the past year

(IF RESPONDENT GIVES ANY OF THE ABOVE RESPONSES, GO TO QUESTION 2)

I did not drink any alcohol in the past year, but I did drink in the past
(GO TO QUESTION 1A)

I never drank any alcohol in my life
(GO TO QUESTION 1B)

1A - During your lifetime, what is the maximum number of drinks containing alcohol that you drank within a 24-hour period? (asked here only of those who did not drink any alcohol during the past 12 months)

- a. 36 drinks or more
- b. 24 to 35 drinks
- c. 18 to 23 drinks
- d. 12 to 17 drinks
- e. 8 to 11 drinks
- f. 5 to 7 drinks
- g. 4 drinks
- h. 3 drinks
- i. 2 drinks
- j. 1 drink

(DONE WITH ALCOHOL QUESTIONS)

1B - So you have never had a drink containing alcohol in your entire life. (asked only of those who say they never drank alcohol in their lives)

Yes, I never drank.

(DONE WITH ALCOHOL QUESTIONS)

No, I did drink

(GO BACK TO QUESTION 1 AND REPEAT)

Question 2 - (asks about number of drinks on typical drinking day in past 12 months)

2. During the last 12 months, how many alcoholic drinks did you have on a typical day when you drank alcohol?
 - a. 25 or more drinks
 - b. 19 to 24 drinks
 - c. 16 to 18 drinks
 - d. 12 to 15 drinks
 - e. 9 to 11 drinks
 - f. 7 to 8 drinks
 - g. 5 to 6 drinks
 - h. 3 to 4 drinks
 - i. 2 drinks
 - j. 1 drink

Question 3 - (asks about maximum drinks in a 24 hour period in past 12 months)

3. During the last 12 months, what is the largest number of drinks containing alcohol that you drank within a 24-hour period?
 - a. 36 drinks or more
 - b. 24 to 35 drinks
 - c. 18 to 23 drinks
 - d. 12 to 17 drinks
 - e. 8 to 11 drinks
 - f. 5 to 7 drinks
 - g. 4 drinks
 - h. 3 drinks
 - i. 2 drinks
 - j. 1 drink

Question 4 - (asks about frequency of maximum drinks in last 12 months)

4. During the last 12 months, how often did you drink this largest number of drinks? Choose only one.
 - a. Every day

- b. 5 to 6 times a week
- c. 3 to 4 times a week
- d. twice a week
- e. once a week
- f. 2 to 3 times a month
- g. once a month
- h. 3 to 11 times in the past year
- i. 1 or 2 times in the past year

Question 5 - (asks about frequency of binge drinking in past 12 months)

5. During the last 12 months, how often did you have 5 or more (males) or 4 or more (females) drinks containing any kind of alcohol in within a two-hour period? [That would be the equivalent of at least 5 (4) 12-ounce cans or bottles of beer, 5 (4) five ounce glasses of wine, 5 (4) drinks each containing one shot of liquor or spirits - to be provided by interviewer if asked.] Choose only one.
- a. Every day
 - b. 5 to 6 days a week
 - c. 3 to 4 days a week
 - d. two days a week
 - e. one day a week
 - f. 2 to 3 days a month
 - g. one day a month
 - h. 3 to 11 days in the past year
 - i. 1 or 2 days in the past year

Question 6- (asks about maximum drinks in 24 hours in lifetime)

6. During your lifetime, what is the largest number of drinks containing alcohol that you drank within a 24-hour period?
- a. 36 drinks or more
 - b. 24 to 35 drinks
 - c. 18 to 23 drinks
 - d. 12 to 17 drinks
 - e. 8 to 11 drinks
 - f. 5 to 7 drinks
 - g. 4 drinks
 - h. 3 drinks
 - i. 2 drinks
 - j. 1 drink

Traditional Marijuana/other drug use (adapted from the National Study of Adolescent to Adult Health)

1. Have you ever used marijuana?
 - a. Yes
 - b. No
2. During the past 30 days, on how many days did you use marijuana?
 - a. Never
 - b. One day
 - c. 2 or 3 days
 - d. 1 day a week
 - e. 2 days a week
 - f. 3-5 days a week
 - g. Every day or almost every day
 - h. Legitimate skip
 - i. Missing
3. Have you ever tried to quit or cut down on your use of marijuana?
 - a. Yes
 - b. No
4. Have you use the following in the past 30 days (for prescription drugs, only answer if you took them without a prescription, took them for longer than prescribed, took larger amounts, or you took them only for the feeling they caused):
 - a. Sedatives or downers (barbiturates, sleeping pills, Quaalude, or Seconal)
 - b. Tranquilizers such as Librium, Valium, or Xanax
 - c. Stimulants or uppers, such as amphetamines, prescription diet pills, Ritalin, preludin, or speed
 - d. Pain killers or opioids, such as Vicodin, OxyContin, Percocet, Demerol, Percodan or Tylenol with Codeine
 - e. Cocaine
 - f. Methamphetamine
 - g. Heroin
 - h. Other- LSD, PCP, ecstasy, mushrooms or inhalants

B. PATIENT HEALTH QUESTIONNAIRE-9

PATIENT HEALTH QUESTIONNAIRE (PHQ-9)

NAME: _____ DATE: _____

Over the last 2 weeks, how often have you been
bothered by any of the following problems?
(use "✓" to indicate your answer)

	Not at all	Several days	More than half the days	Nearly every day
1. Little interest or pleasure in doing things	0	1	2	3
2. Feeling down, depressed, or hopeless	0	1	2	3
3. Trouble falling or staying asleep, or sleeping too much	0	1	2	3
4. Feeling tired or having little energy	0	1	2	3
5. Poor appetite or overeating	0	1	2	3
6. Feeling bad about yourself—or that you are a failure or have let yourself or your family down	0	1	2	3
7. Trouble concentrating on things, such as reading the newspaper or watching television	0	1	2	3
8. Moving or speaking so slowly that other people could have noticed. Or the opposite—being so fidgety or restless that you have been moving around a lot more than usual	0	1	2	3
9. Thoughts that you would be better off dead, or of hurting yourself	0	1	2	3

add columns + +

(Healthcare professional: For interpretation of TOTAL, TOTAL:
please refer to accompanying scoring card).

10. If you checked off <i>any problems</i> , how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people?	Not difficult at all	_____
	Somewhat difficult	_____
	Very difficult	_____
	Extremely difficult	_____

PHQ-9 Patient Depression Questionnaire

For initial diagnosis:

1. Patient completes PHQ-9 Quick Depression Assessment.
2. If there are at least 4 ☐s in the shaded section (including Questions #1 and #2), consider a depressive disorder. Add score to determine severity.

Consider Major Depressive Disorder

- if there are at least 5 ☐s in the shaded section (one of which corresponds to Question #1 or #2)

Consider Other Depressive Disorder

- if there are 2-4 ☐s in the shaded section (one of which corresponds to Question #1 or #2)

Note: Since the questionnaire relies on patient self-report, all responses should be verified by the clinician, and a definitive diagnosis is made on clinical grounds taking into account how well the patient understood the questionnaire, as well as other relevant information from the patient.

Diagnoses of Major Depressive Disorder or Other Depressive Disorder also require impairment of social, occupational, or other important areas of functioning (Question #10) and ruling out normal bereavement, a history of a Manic Episode (Bipolar Disorder), and a physical disorder, medication, or other drug as the biological cause of the depressive symptoms.

To monitor severity over time for newly diagnosed patients or patients in current treatment for depression:

1. Patients may complete questionnaires at baseline and at regular intervals (eg, every 2 weeks) at home and bring them in at their next appointment for scoring or they may complete the questionnaire during each scheduled appointment.
2. Add up ☐s by column. For every ☐: Several days = 1 More than half the days = 2 Nearly every day = 3
3. Add together column scores to get a TOTAL score.
4. Refer to the accompanying **PHQ-9 Scoring Box** to interpret the TOTAL score.
5. Results may be included in patient files to assist you in setting up a treatment goal, determining degree of response, as well as guiding treatment intervention.

Scoring: add up all checked boxes on PHQ-9

For every ☐ Not at all = 0; Several days = 1;
More than half the days = 2; Nearly every day = 3

Interpretation of Total Score

Total Score	Depression Severity
1-4	Minimal depression
5-9	Mild depression
10-14	Moderate depression
15-19	Moderately severe depression
20-27	Severe depression

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C. GENERALIZED ANXIETY DISORDER-7

Generalized Anxiety Disorder 7-item (GAD-7) scale

Over the last 2 weeks, how often have you been bothered by the following problems?	Not at all sure	Several days	Over half the days	Nearly every day
1. Feeling nervous, anxious, or on edge	0	1	2	3
2. Not being able to stop or control worrying	0	1	2	3
3. Worrying too much about different things	0	1	2	3
4. Trouble relaxing	0	1	2	3
5. Being so restless that it's hard to sit still	0	1	2	3
6. Becoming easily annoyed or irritable	0	1	2	3
7. Feeling afraid as if something awful might happen	0	1	2	3
<i>Add the score for each column</i>	+	+	+	
Total Score (<i>add your column scores</i>) =				

If you checked off any problems, how difficult have these made it for you to do your work, take care of things at home, or get along with other people?

Not difficult at all _____

Somewhat difficult _____

Very difficult _____

Extremely difficult _____

Source: Spitzer RL, Kroenke K, Williams JBW, Lowe B. A brief measure for assessing generalized anxiety disorder. *Arch Intern Med.* 2006;166:1092-1097.

D. INFORMED CONSENT

Georgia State University

Informed Consent

Title: The effects of vaping CBD oil on human physiology

Principal Investigators: Rachel Culbreth, PhD and Kyle Brandenberger, PhD

Co-Investigator: Rafaela G. Feresin, PhD

Introduction and Key Information

You are invited to take part in a research study. It is up to you to decide if you would like to take part in the study.

The purpose of this study is to look into how vaping CBD oil affects the body. Your role in the study will last 2 hours over 1 day of testing.

You will be asked to do the following: Fill out surveys of vaping use, breathe into a device to measure lung volumes, cycle on a bike until exhaustion, and provide a small blood sample.

The risks of being in this study include: heart attack, stroke, upset stomach, muscle cramps, bruising, death, dizziness, lightheaded, or tired.

This study is not designed to benefit you. Overall, we hope to gain information about how vaping CBD oil affects the body.

If you do not wish to take part in this study, the alternative is to not participate in this study.

Purpose

The purpose of the study is to look into how vaping CBD oil affects the body. You are invited to take part in this research study because you are a healthy adult between the ages of 18 and 44. A total of 200 people will be invited to take part in this study.

Procedures

If you decide to take part, you will be asked to fill out forms about your health. These forms will tell whether you are healthy enough to be a subject. Then you will fill out a survey about your vaping. These forms will ask about your experience with vaping and CBD oil. In the survey measures, recreational drug use, including illegal substances, will be assessed. This is to inform our assessment of the impact of CBD oil and vaping on your health. You have the right to decline to answer any of these measures, and any questions you do not want to answer may be skipped. Additionally, you can stop this survey at any time.

You will then have your breaths measured with a machine. You will be asked to breathe into the machine normally and very deep and fast. The goal is to measure how well your lungs work.

After this, you will be asked to cycle on a stationary bike while a machine measures your breathing. The cycling will get harder every 2 minutes until you cannot continue. This tests your aerobic fitness.

Finally, you will be asked to provide a small blood sample. A small needle will be used to take about 10 mL of blood from your forearm.

Future Research

Researchers will remove information that may identify you and may use your data for future research. If we do this, we will not ask for any additional consent from you.

Risks

There is the possibility that participation in this study may cause heart attack, stroke, upset stomach, muscle cramps, bruising, death, feeling dizzy, lightheaded, tired muscle cramps. To prevent this, we will ask about your health. If you are at risk for cardiovascular disease you will not be allowed to participate. Tell someone if you experience shortness of breath, headaches, nausea, dizziness, cramps, or lightheadedness and the test will be stopped. Additionally, there is a small risk of infection from venipuncture. These risks will be minimized by cleaning the skin above the vein using alcohol wipes before the procedure. No injury is expected from this study, but if you believe you have been harmed, contact the research team as soon as possible. Georgia State University and the research team have not set aside funds to compensate for any injury.

Benefits

This study is not designed to benefit you personally. Overall, we hope to gain information about how vaping affects the body. This will help the vaping community to understand the risks and benefits of vaping.

Alternatives

The alternative to taking part in this study is to not take part in the study.

Compensation

You will receive \$20 for participating in this study.

Voluntary Participation and Withdrawal

You do not have to be in this study. If you decide to be in the study and change your mind, you have the right to drop out at any time. You may skip questions or stop participating at any time. You may refuse to take part in the study or stop at any time. This will not cause you to lose any benefits to which you are otherwise entitled.

Confidentiality

We will keep your records private to the extent allowed by law. The following people and entities will have access to the information you provide:

- Dr. Rachel Culbreth and her research team.
- GSU Institutional Review Board
- Office for Human Research Protection (OHRP)

We will use a three-digit number rather than your name on study records. The information you provide will be stored locked cabinet, and on password- and firewall-protected computers. A code sheet will be used to identify the research participants. The key will be stored separately from the data to protect your privacy. When we present or publish the results of this study, we will not use your name or other information that may identify you.

Contact Information

Contact Dr. Rachel Culbreth at 404-413-1224 or rculbreth@gsu.edu

- If you have questions about the study or your part in it
- If you have questions, concerns, or complaints about the study
- If you think you have been harmed by the study.

The IRB at Georgia State University reviews all research that involves human participants. You can contact the IRB if you would like to speak to someone who is not involved directly with the study. You can contact the IRB for questions, concerns, problems, information, input, or questions about your rights as a research participant. Contact the IRB at 404-413-3500 or irb@gsu.edu.

Consent

We will give you a copy of this consent form to keep.

If you are willing to volunteer for this research, please sign below.

Printed Name of Participant

Signature of Participant

Date

Principal Investigator or Researcher Obtaining Consent

Date