The Relationship of Driving to Blood THC After Edible Cannabis

By

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Abstract

Smoked cannabis and its impact on driving have been well studied in the past, but there remains a significant knowledge gap regarding the effects of cannabis edibles on driving. This secondary analysis examines correlations between blood cannabinoid levels and driving. Additionally, we investigated the utility of the current per-se limit (2 ng/mL) and median blood THC levels as thresholds for impairment. Blood 11-OH-THC and CBD levels were negatively correlated with measures of speed (Mean and Max Speed, SDSP), indicating that higher levels of these cannabinoids were associated with lower measures of speed. Differences were found in mean speed between placebo and cannabis conditions in the below-threshold groups, but not in the above-threshold groups, suggesting edibles significantly affected speed in the below but not the above group. Research indicates that relying solely on blood THC levels to assess impairment may be insufficient, and suggests that other cannabinoids should be considered as impairment markers.

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A.I. Statement:

The use of A.I. (Artificial Intelligence) was used in the writing process of this M.Sc. Thesis as a tool to aid in the flow of the Thesis and during the editing process. A.I. was not used to generate any text in this Thesis.

1   Introduction

1.1   Rationale

Following the nationwide legalization of recreational cannabis, Canada has become

involved in the emerging research on recreational cannabis consumption[1]. It has been

argued that cannabis use has increased post-legalization[2], due to its increased

availability[2]. This has necessitated ongoing research about the relationship between

recreational cannabis use and its impacts on driving[3]. Epidemiological studies have

established that there are associations between cannabis use and an increased number of

vehicular collisions post-consumption[2-7]. Modern driving simulators have been used to

mimic real-world driving environment, including the visual aspects and environmental

interaction to offer a platform to test drug-impaired driving while ensuring the safety of the

driver and others. These driving simulators typically consists of an instrument cluster,

steering wheel, controls, dashboards and centre console to closely replicate the interior of

modern cars, with large screens surrounding participants to mimic the visual aspect of

driving. Alongside software, simulators can provide the dynamic feedback and allow for a

realistic representation of real-world driving. Initial simulator-based studies using

cannabis strains with low tetrahydrocannabinol (THC) concentrations yielded inconclusive

results[4,8,9]. However, more recent simulator driving studies employing higher THC

concentrations have definitively linked cannabis consumption to changes in driving

behaviors, such as increased variability in lane position ("weaving")[4,10-22], reduced mean

speed[4,13-15,20,22-26], and slowed reaction times[4,14,26-28].

While the majority of current research focuses on the effects of smoked cannabis

on driving, there is a notable gap in the literature regarding the effects of edible cannabis.

Therefore, it is crucial to investigate the impact of edible cannabis on driving performance

measures. Additionally, the current literature on using blood THC levels as a measure of

impairment is inconclusive. Many sources have found no linear correlations between

blood THC and driving impairment[15,19,22,23,27,29-33], while some sources have produced

models predicting such correlations[25,34]. Despite this unclear relationship, many

jurisdictions, including Canada, continue to use *per-se* blood THC levels as an indication

of impairment, even though this has been deemed a poor marker for impairment[35].

Overall, there is a growing body of literature investigating the correlation between

blood THC levels and driving performance. Future research may need to expand beyond

blood THC levels and consider other potential relationships between blood cannabinoids

and driving. Hence, understanding the link between blood cannabinoid levels and driving

performance could be beneficial for developing more accurate and reliable measures of

cannabis impairment, which can inform policy and improve road safety.

1.2   Goals and Hypothesis

1.2.1 Goals:

This analysis is based on a larger study conducted by Zhao et al. 2024[22].

In this analysis, the primary objective was to investigate any association between blood cannabinoid measures and changes in driving performance post-consumption of ecologically valid doses of edible cannabis. Secondary objectives included testing the effectiveness of the current legal cut-off of 2ng/mL blood THC concentration, and the testing of a median split as a threshold for testing effectiveness.

1.2.2 Aims and Hypothesis:

Aim 1: Correlate blood cannabinoid measures (THC, 11-OH-THC, THC-COOH, CBD) and Standard Deviation of Lane Position (SDLP), Mean Speed, Maximum Speed, Standard Deviation of Speed (SDSP), and Reaction Times. *We hypothesize that there will be significant correlations between driving behaviours and blood cannabinoid concentrations following cannabis edible consumption.*

Aim 2: Assess the effectiveness of the commonly used 2ng/mL blood THC threshold in detecting changes in driving measures. *We hypothesize that participants above the 2ng/mL threshold would show a significant difference between cannabis and placebo conditions, while participants under the threshold would not show a significant difference.*

Aim 3: Investigat the median blood THC concentration as a cut-off. *We hypothesize that participants above the median threshold would exhibit a significant difference between the cannabis and placebo conditions, whereas participants below the median threshold would not show a significant difference.*

1.3   Review of the literature

1.3.1 Cannabis Use in Canada

1.3.1.1   History of Cannabis and its legislation

Cannabis sativa, or Cannabis, is one of the oldest plants recorded that has been
cultivated by humans[36]. It has been used in a various ways, including as a source of fiber
for tools and clothing, oil, food[37], and for both medical / recreational purposes, given its
psychoactive properties[38,39]. The first documented cultivation of Cannabis began in Asia
and Egypt almost 5000 years ago and was later introduced into Europe and North America
in 1606[40].

In the 19th and 20th centuries, Cannabis was introduced into Western medicine,
where it was noted for its versatility as a therapeutic agent for pain, muscle relaxation,
sleep, appetite, euphoria, and other illnesses[36]. However, concerns about standardization,
quality control, and dosing led to policy development in Europe in the mid-20th century.
Canada followed suit, prohibiting cannabis in 1923 and adding it to the Confidential
Restricted List within the Opium and Narcotic Drugs Act Amendment Bill[41]. Despite its
prohibition, recreational cannabis use gained popularity, leading to an increase in usage
year after year. It became one of the most used illicit drugs in Canada[42]. Despite efforts to
deter cannabis use through legislation, such as criminalization and harsh sentencing,
usage continued to rise[43].

In 2001, Canada became one of the first countries to legalize and regulate the
medical use of cannabis for specific health issues where traditional therapies proved

ineffective[44]. The Marihuana Medical Access Regulations of 2001 allowed patients to request proper documentation for owning, purchasing, growing, and using cannabis for debilitating medical conditions, with the support of their physicians[44,45]

Nearly two decades later, in October 2018, the Government of Canada passed the Cannabis Act (Bill C-45). This act legalized non-medical cannabis and regulated its production, distribution, sale, possession, and consumption[42]. A year later, amendments were made to include edibles, extracts, and other forms of cannabis[42]. Canada became the second country, after Uruguay, to enact federal legislation legalizing non-medical cannabis and providing legal means to obtain it. Since then, many countries, including Mexico, Georgia, South Africa, and 15 state jurisdictions in the United States, have followed suit in creating similar policies[46]. Many countries have chosen to decriminalize cannabis (i.e., changing possession charges from jail time to a fine) and legalize the use of medical cannabis[47].

1.3.1.2   Demographics of cannabis use in Canada

Non-medical cannabis use in Canada has seen a gradual increase over the past six years since its legalization, although recent years have shown a plateau. In 2018, 22% of Canadians reported using cannabis in the past year, a figure that rose to 26% by 2023[2]. The increase in non-medical cannabis use was influenced by several factors, including the legalization itself and societal changes brought about by the COVID-19 pandemic[48].

Cannabis, being the world's third most commonly used psychoactive drug after alcohol and tobacco (nicotine)[49], has seen a rise in prevalence. This, coupled with the

evolving legislation in Canada, underscores the need to understand the safety and health

implications of cannabis use. The highest prevalence and frequency of cannabis use is

found among 20-24 year olds in Canada, with 48% reporting use in the past year and 23%

reporting daily or near-daily use[2]. Interestingly, the number of individuals who reported

daily use of cannabis, or close to daily, have decreased significantly over the past few

years. In 2021, 29% of individuals aged between 20-24 years old reported daily use,

compared to 23% in 2023[2].

Smoked cannabis, or dried flower, remains a popular choice among Canadian

cannabis users, with 60% reporting use in the past year, although a decrease in flower use

was observed over the past few years[2]. This is the result of an increase in the variety of

cannabis products following the amendment made in 2019 to the Cannabis Act, which led

to a substantial increase in use of other forms of cannabis, such as edibles, vapes, oils,

etc. Edibles are a prime example, as in 2018, 41% of individuals reported using this form of

cannabis in the past 12-months, and in 2023, 54% of individuals reported using edibles[2].

As there has been a clear increase in the number of individuals using edibles, it is

important to explore how edible cannabis differs from smoked cannabis, especially in

relation to driving.

1.3.2 Pharmacology

1.3.2.1   Cannabis and the Endocannabinoid system

1.3.2.1.1   Chemistry of Cannabis

The cannabis plant, particularly its flowering tops and leaves, is a complex organism. It comprises over 500 compounds that fall into 18 distinct classes, including cannabinoids, terpenes, flavonoids, steroids, amino acids, and proteins, among others[40]. Past research has primarily focused on the plant's cannabinoids, with Δ9 -tetrahydrocannabinol (THC), cannabinol (CBN), and cannabidiol (CBD) being the main subjects of study[50-54]. The concentrations of these compounds can vary significantly, influenced by both the strain of cannabis and various environmental factors[50].

In their natural state within the plant, these phytocannabinoids exist in both inactive monocarboxylic acid forms, such as Tetrahydrocannabinolic acid (THCA), and active decarboxylic forms, like THC. When cannabis material is heated above 120 °C, a process known as decarboxylation is triggered, converting the inactive forms into their active counterparts (e.g., THCA to THC). This heating process, which occurs when smoking cannabis, also alters the chemical structure of many other compounds within the plant, thereby modifying their pharmacological effects[50]. Edible products would typically contain the active decarboxylated form of THC obtained from cannabis extracts[55].

While THC and CBD have been the primary targets of past research, many other compounds found in live plants and processed forms have not been studied extensively[50]. As a result, there is limited knowledge about the pharmacological aspects of these

compounds. Some compounds, including terpenes and flavonoids, have been suggested to have broad mechanisms of action, potentially affecting systems beyond the primary physical and psychotropic effects[56]. However, there is minimal research supporting these findings, both in-vitro and in-vivo[50]. Ultimately, cannabis as a plant carries complexity in both chemistry and pharmacology, both of which are slowly being discovered through research.

1.3.2.1.2   Endocannabinoid System

The endocannabinoid system (ECS) is a lipid signaling system that plays a crucial role in regulating various physiological functions in the human body [50,57]. It's linked to the development and regulation of the nervous system, pain management, immune function, appetite, metabolism, and cardiovascular function, among other things[50,58,59]. Dysfunctions in this system can lead to the dysregulation of these physiological functions and may be associated with certain neurodegenerative and psychiatric diseases[58].

The ECS primarily consists of two key receptor components: the cannabinoid type 1 receptor (CB_1R) and cannabinoid type 2 receptor (CB_2R). Both CB_1R and CB_2R are Gi/Go G-protein coupled receptors (GPCRs) that initiate an inhibitory signaling cascade upon activation. In the central nervous system (CNS), CB_1R activation typically results in the inhibition of neurotransmitter release, which results in the inhibition of excitatory and inhibitory synapses. CB_2Rs are associated with complex modulation of immune system functions, and activation of the CB_2R results in downstream modulation of the immune system[60].

CB$_1$ receptors are one of the most common GPCRs in the central and peripheral nervous systems and are most abundantly found in the frontal cortex, hippocampus, cingulate gyrus, cerebellum, and basal ganglia, resulting in the cognition-associated effects of CB$_1$R activation[61,62]. They are also detected in many organs outside the nervous system, including the liver, kidney, skeletal muscles, and bones[61,62]. CB$_2$ receptors are more abundant in the peripheral nervous system, specifically in tissues associated with the immune system, with lower concentrations found in the liver and CNS[63].

The primary activators of endocannabinoid signaling are the cannabinoid receptor ligands N-arachidonoylethanolamine (Anandamide/AEA) and 2-arachidonoylglycerol (2-AG). These are produced through endocannabinoid-synthesizing enzymes as an "on-demand" response to biological stimuli based on the system's requirements and can be inactivated through enzyme-mediated hydrolysis. 2-AG is found at higher concentrations compared to AEA and appears to have a similar preference for both cannabinoid receptors, though it seems to have a higher affinity for CB$_1$R compared to CB$_2$R. 2-AG also appears to bind onto both receptors with greater potency and efficacy compared to AEA[60].

1.3.2.1.3   Pharmacology of exogenous cannabinoids

1.3.2.1.3.1   Pharmacodynamics of THC

THC, an exogenous cannabinoid, acts as a ligand for the Endocannabinoid System (ECS), triggering the activation of the ECS pathway in a manner similar to endocannabinoids. Its primary target is the CB$_1$R, which is linked to the psychoactive effects of cannabis. This is seen in Huestis et al.[64], where they demonstrated that the

administration of a CB_1R antagonist, SR141716 (rimonabant), inhibited the acute psychoactive effects of smoked cannabis.

As a partial agonist of both CB_1R and CB_2R, THC has acute effects in various physiological systems, namely the central nervous system (CNS). In the CNS, acute THC administration is associated with a wide range of therapeutic effects including pain reduction, muscle relaxation, increased appetite, emetic and antiemetic effects, and neuroprotective effects under ischemic and hypoxic conditions[65]. The acute administration of THC can also cause detrimental effects, as cannabis has been associated with several different cognitive effects, including impairment of several cognitive domains, namely memory, attention, concentration and executive function[50,66]. This is of concern, as these cognitive domains are key part of cognition required in the complicated task of driving[67].

1.3.2.1.3.2   Pharmacological effects of THC metabolites

11-Hydroxy-tetrahydrocannabinol (11-OH-THC) is a key psychotropic metabolite of THC, mirroring the effects and kinetic properties of its parent compound. When introduced into the human body via intravenous administration, it exhibits psychoactive effects with a potency equivalent to THC. In animal-based pharmacological studies, 11-OH-THC has shown a potency three to seven times greater than THC[65]. In the current literature, 11-OH-THC has been associated with impairment of several cognitive domains, similar to THC, and is associated with impairing the cognitive processing associated with driving[68,69]. This is important, as the high permeability of 11-OH-THC through the blood brain barrier makes 11-OH-THC a target in future research as a possible marker for detecting impairment.

Conversely, 11-Nor-9-carboxy-tetrahydrocannabinol (THC-COOH) is the primary

non-psychotropic metabolite of THC. It demonstrates anti-inflammatory and analgesic

effects, operating through mechanisms akin to nonsteroidal anti-inflammatory drugs[50].

Intriguingly, THC-COOH has been observed to counter some effects of THC, such as the

cataleptic effect seen in mice, though the exact mechanism behind this remains to be

identified[65].

1.3.2.1.3.3   Pharmacological effects of CBD

Cannabidiol (CBD) is a compound with a wide array of potential applications,

despite its lack of detectable psychoactivity[70]. It exhibits diverse pharmacological actions

and does not seem to bind to either CB1 or CB2 receptors at concentrations that are

physiologically significant. However, it may function as a non-competitive, negative,

allosteric modulator of CB_1 receptors[71], and as a ligand for a variety of targets, including

enzymes, ion channels, and other receptors[72,73].

While CBD does not induce a psychotropic effect, it has been observed to possess

sedative, antiemetic, antiepileptic, antidystonic, and anti-inflammatory properties, which

offer neuroprotection and can counteract the psychotropic and several other effects of

THC[70]. Several studies have found that CBD is associated with enhancements in several

driving-related cognitive domains, including memory and executive function[74-78], while

others have found no significant change in cognition post-consumption[79-81]. While the

literature around the neuroprotective and neuro-enhancing effects of CBD has been

conflicting, continued research on the potential of CBD as a therapeutic may be beneficial.

1.3.2.1.3.4   Pharmacokinetics of Edible Cannabis

In recent years, the market for cannabis products in Canada has seen significant growth, leading to a variety of consumption methods. The method of administration largely influences the absorption and distribution of THC in the body, resulting in a range of biological and subjective effects. The following sections will primarily focus on the pharmacokinetics of THC through edible cannabis, which is the primary focus of this study, and one of the consumption methods growing in popularity in recent years[82].

Absorption: As the absorption of edible cannabis is reliant on the gastrointestinal system, the timeline for the acute effects of cannabis edibles is considerably longer than smoked cannabis. This leads to a more gradual onset of action, lower peak blood levels of cannabinoids, and a longer duration of pharmacodynamic effects, in comparison to smoked cannabis (See Figure 1)[83]. For example, from an oral dose of 20 mg THC in a chocolate cookie, only a small fraction (4 to 12%), of the administered dose enters the systemic circulation, suggesting substantial hepatic first-pass metabolism[84]. The peak blood THC levels of edible cannabis are typically seen 1-2 hours after consumption, with one study reporting that peak blood THC levels were reached at 6 hours post consumption[83]. CBD shares similar characteristics to THC in relation to the variability of its absorption into plasma, resulting in the estimated bioavailability after smoking to range from 11 - 45% [84]. There is a high level of variability in the blood levels of THC and CBD from the consumption of cannabis edibles as there are various factors, including first-pass metabolism[84],the source of the cannabis[83], and the edible medium, affecting how much THC and CBD can reach systemic circulation[50].

Figure 1 provides a clearer visual comparison between smoked and edible cannabis. When consuming a 25mg dose, smoked cannabis reaches peak blood THC concentration within 10 minutes, with levels rising to about 10ng/mL, as shown in the graph by Spindle et al. (Figure 1, left). In contrast, for edibles at the same 25mg dose, it takes approximately 2 hours to reach peak blood THC concentration, which is much lower, around 2.5ng/mL, as illustrated by Vandrey et al. (Figure 1, right). Additionally, THC from edibles remains detectable in the blood for a significantly longer period, with traces persisting up to 26 hours post-consumption, although these factors may vary depending person-to-person.

Figure 1: Comparison of Blood THC levels of Smoked and Edible Cannabis (from Spindle et al.[85](Left), and Vandrey et al.[86](Right)
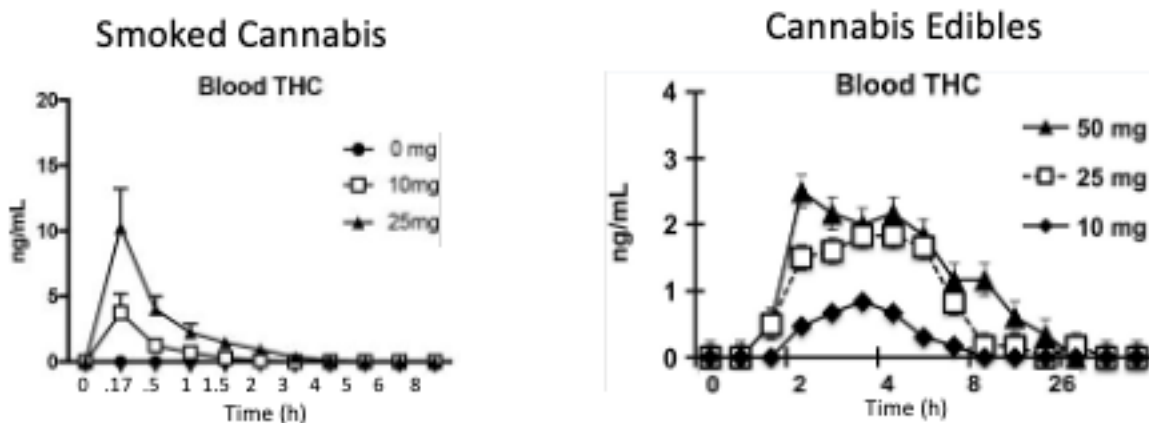
Distribution: After THC enters the bloodstream, a gradual decrease in plasma concentrations of THC is observed after edible cannabis consumption. Factors such as body size, frequency of use, disease states, and composition influence the distribution of cannabinoids[87,88]. Due to the highly lipophilic nature of THC, it is primarily absorbed by fatty

tissues and organs with high perfusion rates, such as the brain, heart, lung, and liver[83]. The

apparent volume of distribution of THC is large (~10 L/kg), which can be attributed to its

high lipid solubility[50]. Residual THC in plasma, likely originating from adipose stores in the

body, can be detected weeks after consumption[89], and potentially associated with

persistent psychomotor impairment in frequent chronic cannabis smokers[89]. Despite the

high perfusion level of the brain, the blood-brain barrier appears to limit the access and

accumulation of THC in the brain[83]. The delay in correlating peak plasma concentration to

psychoactive effects may be attributed, in part, to the time required for THC to traverse this

barrier[90].

Metabolism: Edible cannabis significantly differs from smoked cannabis, as first-

pass metabolism by the liver plays a large role in the metabolism of cannabis edibles. This

is because cannabinoids reach the liver before exerting their biological effects. This first-

pass metabolism results in a generally lower plasma concentrations of THC and 11-OH-

THC when compared to smoked cannabis. When THC enters the bloodstream, it

undergoes oxidation by the cytochrome P450 (CYP) oxidases CYP2C9, CYP2C19, and CYP

3A4, primarily in the liver but also in extra-hepatic tissues such as the gastrointestinal tract

and the brain[83,90]. The primary metabolites of THC include the active compound 11-

hydroxy-Δ 9 -tetrahydrocannabinol (11-OH-THC) and the inactive compound 11-Nor-9-

carboxy-Δ 9 -tetrahydrocannabinol (THC-COOH)[83,91].

CBD follows a different set of metabolic pathways from THC, as it goes through

extensive Phase I metabolism to produce upwards of 30 different metabolites in the

urine[83]. The most abundant metabolites are hydroxylated 7 (or 11)-carboxy derivatives of CBD, with 7 (or 11)-hydroxy CBD being a minor metabolite[83].

Elimination: Post-consumption, the elimination of THC and its metabolites primarily takes place through feces and urine [83]. The average whole-body clearance of THC and its hydroxy metabolite is around 0.2 L/kg-h, although this can vary significantly due to the intricate nature of cannabinoid distribution[92]. Research has shown that within 72 hours, fecal samples can reveal up to 50% of a THC dose labeled with radioactive markers, while urine samples only account for 10-15% of the same dose[83,93]. The exact elimination half-life of THC and CBD is challenging to calculate because the equilibrium of the rediffusion of them from adipose to plasma is reached slowly, resulting in very low plasma concentrations that are difficult to measure for an extended period of time[65].

1.3.3 Cannabis use and Driving

Given the pharmacokinetics and pharmacodynamics of cannabis, its impact on driving-related cognitive functions is a serious safety concern, as THC, CBD, and their metabolites affect not only the central nervous system (CNS) but also the peripheral nervous system (PNS) and other organs. High concentrations of CB1 receptors, which are linked to cannabinoids' psychoactive properties[64], are found in brain regions integral for cognition: the temporal lobe, cerebellum, and neocortex[63,94]. Consequently, cannabis use has been implicated in cognitive abnormalities that impair crucial driving abilities such as attention span, working memory capacity, and cognitive control processing[95,96]. Given that driving demands intricate coordination between cognitive processes as well as visual-

motor skills[70], the acute decrease in cognitive function following edible cannabis consumption poses significant risks. This is notable because while peak psychoactive effects manifest within two hours post-use, studies indicate residual impairment can persist for several hours or even up to 24 hours later[95]. Considering these findings alongside individual pharmacological variances[68] and differences stemming from dosage or administration method, the implications for road safety when individuals drive after consuming cannabis cannot be underestimated.

Overall, cannabis has been associated with decreased alertness, reduced attention span, impaired response times, and reduced accuracy of motor responses[97]. Because of these effects, activities like driving a motor vehicle while under the influence of cannabis can be very dangerous[98], though the negative impact of cannabis on driving performance increases with higher dose and decreases with time since use[99]. THC has been shown to decrease driving ability as by decreasing general cognition, cannabis-impaired drivers are less able to react appropriately to adverse/dangerous events[100].

1.3.3.1   Epidemiological Studies

Epidemiological studies help shed some light towards the cause and effect of the risks associated with impaired driving in real-world scenarios, more specifically, looking into the factors associated with Driving Under the Influence of Cannabis (DUIC). Several factors are commonly mentioned as problematic in DUIC literature, including crash risks and injury risks.

While earlier evidence on the crash risk associated with cannabis consumption were inconclusive[4], much of the recent literature point to cannabis consumption being associated with crash risk. For example, a 2019 study from British Columbia of over 3000 drivers presenting to trauma centers following a motor vehicle collision, found that 8.3% of drivers were cannabis positive[101]. Other studies have found similar findings of crashes while under the influence of cannabis, with some pointing to an increase in the prevalence of drivers with detectable levels of blood THC who end up in hospitals due to their injuries[101-105]. While these studies only focus on the detection of THC in systemic circulation, they do not consider whether cannabis is the main culprit behind the accidents, but these studies provide a point of data to understand that THC is being detected in blood in an increasing number of accidents. But overall, systematic reviews and meta-analyses of DUIC point towards the conclusion that acute cannabis consumption is associated with an increase in traffic crash risk, considering the odds ratio of 1.36 to 2.66[3,6,7,106,107].

1.3.3.2   Laboratory studies

Laboratory studies offer a direct method for assessing the impact of drugs, such as cannabis, on driving skills. Participants are tested before and after cannabis consumption, providing a clear before-and-after comparison. With advancements in technology, driving simulators and virtual reality have become valuable tools for scientists. These technologies closely mimic real-world driving experiences, enabling more accurate testing of drug-impaired driving while minimizing the risks associated with real-world impaired

driving. Simulators also offer a more sensitive platform for tracking changes in driving

behavior that might not be observable in real-world scenarios.

Present laboratory studies, utilizing driving simulators, consistently demonstrate

that acute cannabis consumption induces alterations in driving measures, indicating an

increase in 'weaving' or the standard deviation of lateral position (SDLP)[4,10-22], a decrease in

mean speed[4,13-15,20,22-26] and a slowed reaction time[4,14,26-28], though no discernible effects

have been detected on brake latency[4,14].

Despite numerous studies examining the impact of cannabis on driving measures,

the relationship between blood THC levels and driving impairment remains inconclusive.

While some research, such as Hartman et al., have made models that predicted higher

blood THC levels correlate with decreased mean speed, increased following distance[25],

and increased SDLP[34]. However, multiple studies have found no definitive correlation

between blood THC levels and changes in driving measures[15,19,23,29-33]. Instead, the current

literature points to a dose-response relationship, where the amount of THC consumed,

rather than blood THC levels, is linked to changes in driving performance, including SDLP,

speed, and reaction time[4,23,26,34,108]. Therefore, due to the inconclusive findings of the

current literature, further research into alternative relationships between biological

measures and driving impairment is needed, possibly through the use of THC metabolites

and other lesser-known cannabinoids, as well as detection through saliva.

1.3.4 Relevance of Research

It is important to note that the majority of existing studies have primarily focused on

the impact of smoked cannabis on driving. As of now, with the exception of the parent

paper for this analysis[22], no studies have explored the acute effects of edible cannabis on simulated driving or the correlation between blood cannabinoid levels and alterations in driving measures after cannabis edible use. Adjacent to cannabis edibles, there are several studies that have investigated the use of oral synthetic cannabis and driving[4,11,21]. These studies investigated the use of dronabinol, a synthetic formulation of THC, and had found that the consumption of oral dronabinol was associated with increases in SDLP [11,21] and worse reaction time[21] in a dose dependent manner, but no significant effect was seen on measures of speed[11], gain or coherence[21]. A more recent study investigating the effects of 10mg of oral dronabinol had found no significant changes in SDLP and mean speed 100- and 210-minutes post-consumption when compared to placebo[109]. The use of these studies can help shed light on the impact of cannabis edibles on driving, as they share a similar route of administration.

In Canada, *per-se* laws establish specific blood THC limits to determine impairment while driving, with thresholds set at 2 nanograms per milliliter (ng/mL) for a summary conviction offense and 5 ng/mL for a summary conviction or indictable offense[110]. However, these limits are controversial due to inter-individual differences in the subjective effects of cannabis as well as the poor relationship between blood THC levels and driving impairment, mentioned previously. The current thresholds of 2 ng/mL and 5 ng/mL may be unreliable, potentially causing false positives and false negatives. For instance, cannabis edibles can result in prolonged blood THC detection many hours after consumption, even when drivers no longer feel the subjective effects. Ultimately, the use of the *per-se* blood THC levels may unfairly penalize unimpaired drivers who consumed cannabis previously

and may fail to identify genuinely impaired individuals. This study investigates the use of

the 2ng/mL threshold and may identify whether the use of the threshold can correctly

identify driving impairment.

The rise in edible cannabis consumption has highlighted the need for targeted

research into impairment detection following its use[2]. Unlike smoked or vaped cannabis,

edibles have a unique pharmacology, making much of the existing research on cannabis

and driving less applicable. Understanding the effects of edibles on driving is critical, as

studies have shown significant behavioral impairments, even when blood THC levels are

low[111,112]. This presents challenges for roadside detection, as THC levels in the blood after

consuming edibles are generally much lower than those observed with smoking, often

below the current *per-se* Blood THC levels. Current methods, such as the Standardized

Field Sobriety Test (SFST) and per-se blood THC limits, often fail to accurately detect

impairment from edibles, leading to false positives or negatives. Due to these limitations,

alternative detection methods are needed[113]. Previous research found oral fluid THC levels

of 100 ng/mL after consuming a 10 mg cannabis-infused brownie, which far exceeds the

current saliva cut-off of 25 ng/mL[31]. Based on this, the parent study investigated the

possibility that saliva tests are a more reliable indicator of recent edible use. However, the

study found that saliva tests were largely ineffective, as only 4 out of 22 participants tested

positive for THC two hours after consumption. One possibility is that the low dose

consumed (7.3 mg THC) may explain the lack of positive results, but the study raised the

possibility that commercial edibles, limited to 10 mg per packet, may enable users to

ingest cannabis without detection. This issue underscores the need for further research and improved detection strategies for edibles.

2   Methods

This was a within-subject. counterbalanced, observational human laboratory experiment conducted at a single site in Toronto, Ontario, Canada at the Centre for Addiction and Mental Health Ursula Franklin Site. This study was approved by the Centre for Addiction and Mental Health (CAMH) Research Ethics Board (#042/2021) and the Health Canada Research Ethics Board (2020-043H). The study was conducted at CAMH in Toronto, Canada. Participants were recruited between November 2022 and April 2023, with no follow-up period.

2.1   Study Overview

This human participant study followed a within-subject, counterbalanced, observational study design with ecologically valid doses of cannabis, as participants were asked to bring and consume their own legally purchased cannabis edibles. This study was designed to study the effects of edible cannabis on simulated driving and on blood cannabinoid levels. Participants were invited to the Centre for Addiction and Mental Health (CAMH) for a total of 3 sessions. Session one consisted of an eligibility assessment and an opportunity for participants to familiarize themselves with the driving simulator, subjective and cognitive assessments. Sessions two and three were the test sessions scheduled during session

one, with a washout period of at least 72 hours between. Participants were instructed to bring in their preferred legal edible for the cannabis test session, at the dose and strength equivalent to their normal use. Participants consumed a candy during the non-cannabis session, in the form of a chocolate or gummy candy. Other than drug treatment, both cannabis and non-cannabis sessions were identical in format. As this was a counterbalanced study, a randomization schedule was generated through computer software, and the order of the test sessions were determined through the randomization schedule. Since this was a study with high ecological validity, no blinding of the participants or the study staff was undertaken. Timeline in Table 1 represents when assessments were conducted throughout a test session day.

2.2   Participants and Screening

Participants from previous studies who were interested in participating in future studies were re-contacted for the recruitment of this study. To mitigate potential effects of practice, participants were excluded if they had previously participated in a similar simulator study. Participants were given an online eligibility screening questionnaire, which included age, driver's license class, details of cannabis use, willingness to purchase their preferred cannabis edibles to the study, willingness to abstain from cannabis for 72 hours and from alcohol and other psychoactive/recreational drugs for 12 hours prior to test sessions.

2.3   Eligibility Assessment and Consent

Participants who met the eligibility criteria based on the online screening questionnaire were subsequently contacted to arrange an eligibility assessment visit. Participants received instructions on the meeting location for their session and were sent a copy of the consent form via email. This early communication allowed participants to review all relevant study information before the eligibility visit. Upon arrival, study personnel discussed the consent form with the participant, addressing any questions they might have had about the informed consent document. After signing the consent document, participants completed a short quiz to ensure their understanding of the details of the consent document. The quiz consisted of 10 questions, and if a participant scored 7 or lower, participants were asked to read through the consent again before retaking the test. If participants scored 7 or lower again, the participant was excluded from the study. During the visit, study personnel also collected information on concomitant medications to verify that none of the prescribed drugs had contraindications with cannabis.

2.4   Practice Session

During the same eligibility assessment visit, participants were given the opportunity to experience the cognitive, subjective and driving assessments used during the test session visits. Data collected during this visit was not included in the analysis. Participants were asked to operate the simulator through several practice scenarios similar to the driving scenarios used during the test session visits. As it was known that the simulator caused

nausea and sickness in some participants, in the event where participants felt sick, they were given a break and some water before attempting to operate the simulator again. If further sickness was observed, the participant would not continue with the study. Test session visits were scheduled at the end of this visit.

2.5   Test session

Participants completed two test sessions in a counterbalanced order. One session involved active cannabis that participants brought with them, while the other session was conducted without cannabis. During the non-cannabis session, participants received a candy replacement equivalent to the form of edible cannabis chosen for their active cannabis session.

For the active cannabis session, product information such as the cannabis edible brand, strain, and THC/CBD contents were recorded. This data was obtained through a visual inspection of the packaging and compared with the online depiction of the product via the Ontario Cannabis Store (OCS).

At the beginning of each session, study personnel confirmed ongoing eligibility by conducting breathalyzer, saliva, and urine tests. These tests ensured abstinence from alcohol for 12 hours, abstinence from cannabis for 72 hours, and abstinence from other psychoactive drugs. In case of a positive result, sessions were rescheduled. Female participants under the age of 65 also underwent urine pregnancy tests.

Information about recent cannabis use was collected using a timeline follow-back checklist, where participants recalled their cannabis use in the 7 days prior to the test session, and study personnel recorded the dose and form of cannabis consumed.

Participants were instructed to fast before the test session and were provided with a light breakfast and lunch consisting of low-fat options, as pre-clinical studies have shown that high-fat foods can increase systemic exposure of THC and CBD several fold when compared to lipid-free formulations when cannabis is administered orally in rats[114].

Baseline measurements were taken before treatment, which included vitals, blood and saliva samples. The blood samples were used to quantify the concentration of THC, CBD, and metabolites of THC. Participants then completed driving trials, as well as cognitive and subjective assessments, which served as the baseline measurements.

After collecting baseline data, participants consumed either the edible cannabis or the control candy and were given time to acclimate. Driving trials occurred approximately 120, 240, and 360 minutes after treatment consumption. Blood samples were collected around 120 minutes after treatment ingestion, just before the 1st driving after consumption. At the end of the cannabis session, participants were sent home in a taxi and provided tokens for public transportation for their trip to the study site. Participants were not sent home in a taxi for the non-cannabis session, and were provided tokens for public transportation for their trip to and from the study site

Table 1. Schedule of Measures collected throughout sessions

Measures		Session 1 Practice Session	Session 2 and 3 (Test Sessions)								
			Time Pre/Post Cannabis Edible Consumption (minutes)								
			Baseline (-120 minutes)	30	60	120	180	240	300	360	420
	Consent	X									
	Timeline Followback (7-days)		X								
Ongoing Eligibility	Breathalyzer for Recent Alcohol use		X								
	Point-of-care Saliva		X								
	Urine Toxicology Screen		X								
	Urine Pregnancy Test (If Applicable)		X								
	Driving Trial	X	X			X		X		X	
	Blood test for THC and Metabolites		X				X				
	Vital Signs (Pulse, Blood Pressure)		X	X	X	X	X	X	X	X	X

2.5.1 Inclusion criteria

The following are criteria that participants must follow to be eligible for this study:

- Adults aged 19 to 79 years (19 is the legal age to consume edibles in Ontario; the upper limit is to mitigate against illness and frailty associated with ageing)

- Users of cannabis who self-report using a cannabis edible at least once in the last 6 months

- Holds a valid G or G2 Ontario driver's licence (or equivalent from another jurisdiction for at least 12 months)

- Willing to abstain from alcohol and other drugs (other than nicotine and drugs required for treatment of a medical condition) for 12 hours prior to study session

- Willing to provide and consume a legally purchased edible in the lab during the test session

- Willing to abstain from cannabis for 72 hours prior to the other test session

- Must drive at least once a month

- Provides written and informed consent

2.5.2 Exclusion criteria

- Currently pregnant or breastfeeding (for the safety of the fetus)

- Taking medications or have any medical condition that may affect driving or for which cannabis is contraindicated, including opioids for pain

- Participation in other research studies

2.5.3 Ongoing eligibility

The following eligibility criteria were confirmed at the beginning of each test session in an ongoing basis, if tested positive, participants were excluded from the study, or the visit would be rescheduled:

- Alcohol use within the 12 hours before session

- Cannabis use within 72 hours before session

- Use of other psychoactive drugs not prescribed leading to a positive point-of-care test.

2.5.4 Abstinence of Cannabis

The current study assessed 72-hour cannabis abstinence through a combination of point-of-care saliva and self-report questionnaires. Determining the exact timing of past cannabis use can be challenging due to various individual factors, including the participant's history of cannabis use. For instance, low levels of THC and its metabolites might be detected in the urine of chronic users even weeks after consumption[83]. This makes urine testing potentially ineffective for confirming 72-hour abstinence, but it can still be used as an indication of prior cannabis use. On the other hand, saliva testing has been recognized in previous studies as a more reliable measure of recent cannabis use [83]. It was previously reported that THC had been detected in saliva up to 13.5 hours after smoking [115], with a rare case reporting trace amounts detected up to 72 hours after smoking in a high frequency chronic cannabis smoker[116]. Therefore, the combination of

point-of-care saliva tests and self-report questionnaires were deemed adequate for determining cannabis abstinence in this study.

2.6   Collected measures

2.6.1 Simulated Driving Trials

Simulated driving scenarios were used to assess the overall driving performance of participants. Participants were asked to drive a total of 4 driving trials throughout a test session visit. These driving trials consist of 3 separate scenarios, each lasting for approximately 10 minutes, for a total of approximately 30 minutes, depending on the driving speed. Single task driving scenarios included a series of potentially frustrating driving events and uneventful highway driving on a two-lane rural highway, which were used to assess the driver's speed, lateral control, and collisions using the Virage VS500M driving simulator's software.

To better simulate real-world driving conditions and the cognitive load associated with it, the dual task driving condition introduced a counting task while driving the scenario. This dual-task condition consisted of the participant being asked to count backwards by threes from a random large 3-digit number, selected by study personnel at the beginning of the driving trials. This backwards counting task has been validated in previous driving studies as an effective methodology to mimic real-world distractions.[117,118]

The third driving scenario was used to assess driver's reaction time in terms of brake pedal latency. This scenario consisted of an endless 4-lane highways where participants were instructed to drive at 100km/hr, while remaining in the second lane to

the right. When presented with a stop sign facing them (labelled a 'true stop sign'), participants were to come to a complete stop as quickly as possible. When presented with a stop sign facing away from them (labelled a 'false stop sign'), participants were to maintain their speed. During each of these reaction time scenarios, a total of 10 stop signs appeared suddenly at the far-right lane, 7 of them were true and 3 of them were false.

2.6.2 Measures collected from simulated driving trials

- Standard deviation of lateral position (SDLP)
  - This is a measure of the amount of lane deviation or "weaving" (in centimeters) that is seen during the driving trials and has been previously found to be sensitive to the effects of psychoactive drugs on driving and has been associated with cannabis use previously[4,10-22].
- Mean speed (MS)
  - This is a measure of the average speed (in kilometers per hour) observed during the driving trials. Individuals often exhibit a compensatory effect after the consumption of cannabis, as the awareness of impairment after cannabis use results in decreases in driving speed[67].
- Standard deviation of speed (SDSP):
  - This is a measure of the change or variability in speed during the driving trial. SDSP can be used to determine the driver's ability to remain at certain speeds.

- Maximal speed (MAX):

    - This is a measure of the maximum speed observed during the driving trial. Similar to mean speed (MS), measures of speed are often affected by cannabis use due to the compensatory effect[67].

- Reaction Time:

    - This is a measure of the reaction speed of the participant during a driving trial, as it uses brake latency (in milliseconds) to represent reaction time. It is measured by the calculating the amount of time between when the participant initiates the brake pedal, and the appearance of the true stop sign during the reaction time driving trial.

- Number of collisions: This measure represents the number of times the participant's vehicle collides with an obstacle during the driving trial (Another vehicle or another object). This is recorded by study personnel during the driving trial.

2.6.3 Driving Simulator

The driving simulator that was used for this study was a VS500M simulator manufactured by Virage Simulations Inc.[119]. This simulator consists of a driver's side instrument cluster, steering wheel, controls, dashboard, and centre console that replicates a compact car from General Motors. All the components of the simulator are programmed to provide dynamic feedback to the driver, to display realistic representations of the driving to the

driver and are designed to interact as if it were operating a real vehicle. This would include realistic force feedback in the steering wheel and pedals, as well as a three-axis motion platform that can simulate acceleration/deceleration, engine rumble, and road texture. The visual system consists of three 55-inch screens providing a 180° field of view in the front, and two 17-inch side displays providing visual feedback for the left and right blind zones, which allow the driver to properly monitor their visual surroundings while driving.

2.7   Other Assessments

2.7.1 Alcohol Breath sample

A breathalyser (Alert J5) breath test was administered to check the breath alcohol concentration at the start of all sessions, including the practice session. In the case that a non-zero reading was displayed, which indicated that the participant was under the influence of alcohol, they would be rescheduled or excluded from the study. The breathalyzer used for the study was calibrated annually by the CAMH clinical laboratory

2.7.2 Urine Toxicology and Pregnancy Testing

Urine toxicology screenings were completed at the beginning of the test session visits to confirm ongoing eligibility of abstinence of other non-prescribed psychoactive drugs. This screening was completed by a study personnel with a point-of-care urine cup and through a visual inspection of the test strips. In the case that the point-of-care urine cup showed a

positive result for any of the other substances, participants were rescheduled or

withdrawn from the study. Pregnancy tests were completed with female participants under

the age of 65 to ensure that participants are not pregnant during the study. Pregnancy tests

were completed at the same time as the urine toxicology screening. A positive pregnancy

test resulted in the participant being withdrawn from the study.

2.7.3 Vital signs

Vital signs were used to monitor the participant throughout the duration of the study.

Measures that were collected included heart rate and blood pressure. Vital signs were

taken only during the test sessions at baseline, 30 minutes after consuming the edible, and

hourly from one hour to seven hours after cannabis consumption.

2.7.4 Blood Measurements (from Di Ciano et al. 2024)[15]

Each sample of blood (10mL) was collected in a lavender top test tube and transferred to

cryotubes to be stored in the freezer (-80 degrees Celsius) until shipment to the blood processing

facility (Dynacare). Extraction and analysis of THC, COOH-THC, OH-THC and CBD in whole blood

was performed according to a method developed in-house by Dynacare. Briefly, 100 µL of each

sample was mixed with methanol containing the Cannabinoids Working Internal standard (IS),

allowing for precipitation. Samples were vortexed for 60 seconds, then allowed to equilibrate at

room temperature for 10 minutes. Subsequently, samples were centrifuged at 4500 RPM for 5

minutes. The supernatant was transferred into an HPLC vial and injected onto the Prominence

HPLC System (Shimadzu) followed by subsequent analysis on the 6500+ QTRAP LC-MS/MS

(SCIEX). All analytical data were collected and processed using Analyst 1.6.2. The concentration of cannabinoids in the samples were determined using linear regression with a weighting factor of 1/x. The limit of quantitation (LoQ) for all cannabinoids was 0.2 ng/mL, with an analytical measuring range of 0.2 to 500 ng/mL. For all samples with values of < 0.2 ng/mL a value of 0.1 ng/mL was substituted for analysis.

2.7.5 Saliva test

Saliva point-of-care tests were administered by study personnel at the beginning of the test session visits to confirm ongoing eligibility of abstinence of cannabis.

2.7.6 Sample Size

This observational study is among the first to explore how cannabis edibles affect driving and the relationship between THC concentrations in blood and saliva. It serves as a proof-of-concept for future larger-scale research. The sample size of 20 participants was based on previous studies involving smoked cannabis, where changes in SDLP and mean speed informed the calculation. For example, Di Ciano et al. (2020) observed significant changes in mean speed in a pilot study with 14 participants[120], while Fares et al. (2022) noted significant SDLP changes in a study with 28 participants[121]. To account for about 15% attrition, ensuring an 80% power with an alpha of 0.05 and a medium effect size, a sample size of 24 was deemed necessary. Ultimately, 22 participants completed all study procedures.

2.7.7 Cannabis Edibles

This study was an observational study that aimed to understand the safety of legally available cannabis in Canada, more specifically, the effects of cannabis edibles on driving, at the dose and potency that participants normally use. Participants were asked to bring the edible in their original sealed packaging to confirm that the cannabis was indeed legally purchased, as well as collecting information about the cannabis edible itself, like the brand, potency of THC and CBD, and purity of cannabis. At the time of consumption during the study, the number of cannabis edibles consumed was verified by study personnel to assess the dose of THC and CBD consumed. Because of the presence of both THC and CBD in the cannabis edible products that were brought in by the participants, THC, CBD, and its metabolites would be measured in the blood to confirm their presence.

2.8   Statistics/Data analysis

2.8.1 Data collection and extraction

At the end of each session, all driving data was collected, with a backup copy created to safeguard against data corruption. The simulator provided raw data for SDLP, Mean Speed, Maximum Speed, SPSD and reaction time for both single-task and dual-task drives. This data underwent post-processing, as it was organized by session visits, prior to its use in the statistical analyses. The four driving measures from the single and dual-task driving trials were recorded at a rate of 10 frames per second, given their lower fidelity

requirements. The reaction time driving measure was captured at 60 frames per second due to the need for higher fidelity in tracking the time interval between the appearance of the true stop sign and the moment the brake was pressed. Study personnel manually calculated this time interval before incorporating the data into statistical analysis. IBM SPSS Statistics 27.0 for Windows was used for all statistical analysis.

2.8.2 Contrasts of the outcome measures between the Cannabis group and placebo group at 120min, 240min and 360min. (From Zhao et al. 2024)

To account for the correlation of repeated measures on the participants, mixed-effect models using Time (120 min, 240 min, 360 min), Treatment (No Cannabis vs Cannabis), and their interaction as fixed effects, and individual participants as random effects, were adjusted to all outcome measures. The models for the outcome measures also controlled for session order (the sequence of smoking cannabis or no cannabis), baseline blood THC, and the baseline value of the outcome measure. The contrasts of the least square means of the outcome measures between the treatment groups Cannabis-No Cannabis at each time point for driving and blood THC, CBD, and metabolites of THC (11-Nor-9- -THC (COOHTHC) and 11-hydroxy-THC (THC-11-OH)).

This analysis, completed by a CAMH statistician, is part of a larger study (Zhao et al. 2024), which provided an overview of the changes observed in driving measures and blood cannabinoid levels following the consumption of cannabis edibles.

2.8.3 The correlation between blood levels of THC with driving outcomes in the cannabis group.

As understanding the relationships between blood THC levels with changes in driving measures is one of the main goals of this study, it was of interest to investigate the correlation between these relationships. The correlations of SDLP, mean speed, max speed, SDSP and reaction time with blood THC, 11-OH-THC, THC-COOH and CBD, as well as dose of THC in the cannabis group at 120min were tested with correlation analysis (Spearman's rank-order correlation).

2.8.4 Testing the effectiveness of the 2ng/mL cut-off in detecting changes in driving measures

Given the interest in assessing the efficacy of the blood THC level cut-off, it was of interest to determine if there were significant differences in driving measures between participants over and under the legal THC limit. For this analysis, all driving measure data were bifurcated into two groups: one comprising participants with a blood THC level exceeding 2 ng/mL, and the other with participants having less than 2 ng/mL of THC in their blood. Analysis was conducted between the placebo and cannabis conditions for each cut-off utilizing the Wilcoxon signed-rank test. Effect size between placebo and cannabis conditions were calculated through the Wilcoxon and were used to evaluate any meaningful differences between the conditions. This analysis included all driving measures from both single-task and dual-task drives and reaction time. The difference

between the above and below cut-off groups (Cannabis-placebo condition) was analyzed with a Mann-Whitney U test, followed by effect sizes.

2.8.5 Investigating the median blood THC concentration as a cut-off

Considering the significant variability in blood THC concentrations among participants, we were interested in examining the use of median blood THC concentrations as a comparison to the legal THC cut-off of 2ng/mL. For this analysis, we categorized the data on driving measures into two groups based on a median split of 2.3 ng/mL blood THC concentration, measured 120 minutes after cannabis consumption. This categorization resulted in two participant groups - one with blood THC levels above the median, and the other below. Analysis was conducted between the placebo and cannabis conditions for each cut-off utilizing the Wilcoxon signed-rank test. Effect size between placebo and cannabis conditions were calculated through the Wilcoxon and were used to evaluate any meaningful differences between the conditions. This analysis included all driving measures from both single-task and dual-task drives and reaction time. The difference between the above and below cut-off groups (Cannabis-placebo condition) was analyzed with a Mann-Whitney U test, followed by effect sizes.

3   Results

3.1   Demographics

Demographics for all participants who completed this study are presented in Table 2. As

this study had a within-subject, counterbalanced design, all participants were part of both

the cannabis and non-cannabis sessions.

Table 2. Participant Demographics

Total Participants	N = 22
Sex N (%)	16 Male (73%) 6 Female (27%)
Mean Age (SD)	47.59 (22.2)
Age Range	19-74
Years Using Cannabis (SD)	21 (20.7) Range: 1 - 58 years
Frequency of cannabis use	more than once a day - 4 once a day - 8 5-6 times a week - 2 3 - 4 times a week - 3 twice a week - 1 once a week - 1 2-3 times a month – 2 Once every 3-6 months - 1

Reasons for using cannabis	Medical - 1
	Recreational - 19
	Both - 2

3.2 Adverse Events

No adverse events were recorded during the test sessions of the study. During the practice

session visit, 3 participants were removed from the study due to them experiencing

simulator sickness.

3.3 Test Session Cannabis Consumption and Dose

In this study, participants predominantly favored gummies as their edible choice (n = 17).

However, there were exceptions: 3 participants opted for chocolate, 1 participant selected

a cookie, and 1 participant selected a brownie. Notably, over half of the consumed

products primarily contained THC with negligible amounts of CBD (n = 13), while the

remaining products exhibited a combination of both THC and CBD. The average THC

content across all consumed cannabis edibles was 7.295 ± 2.856 mg, and the average

CBD content was 2.168 ± 3.624 mg.

Table 3. Breakdown for dose of THC and CBD in consumed cannabis edibles and types of

edibles consumed by each participant. Listed in ascending order of dose of Δ9-THC and

CBD (mg).

Participants	Δ9-THC (mg)	CBD (mg)	Type of cannabis Edibles
1	2	2	gummy
2	4	0	gummy
3	4	0	gummy
4	4.5	5	gummy
5	5	0	gummy
6	5	0	gummy
7	5	0	gummy
8	5	5	gummy
9	5	5	gummy
10	5	10	gummy
11	6	0	gummy
12	10	0	chocolate
13	10	0	gummy
14	10	0	gummy
15	10	0	gummy
16	10	0	gummy
17	10	0	gummy
18	10	0	gummy
19	10	0	brownie
20	10	0	cookie
21	10	10	chocolate
22	10	10	chocolate
Average	7.295	2.136	
St.Dev.	2.856	3.642	

3.4   Blood Cannabinoid Concentrations

In general, blood levels of THC, 11-OH-THC, THC-COOH, and CBD have been found to

increase after cannabis consumption. A Student's Paired T-test was used to analyze the

differences between the cannabis and no cannabis condition and found that blood THC,

11-OH-THC and THC-COOH are significantly higher in the cannabis condition when compared to the no-cannabis condition at 120 minutes. (THC: $t(21) = -4.401$, $p = < .001$, 11-OH-THC: $t(21) = -6.494$, $p = < .001$, THC-COOH: $t(21) = -3.467$, $p = 0.002$) Blood CBD levels did not show statistically significant differences between cannabis and no-cannabis conditions ($t(21) = -2.05$, $p = 0.053$). No significant statistical differences were observed in the before treatment comparison. See table 4.

Table 4: Means (SD) of Blood Cannabinoid Levels at baseline (Before) and at 120 minutes (After) post-consumption of Cannabis Edible (Cannabis Session) or control candy (No Cannabis Session). Comparison of Cannabis to No Cannabis session analyzed using Student's Paired t-test * $p < 0.05$, different from no cannabis for that time point.

Mean Blood Cannabinoid Levels								
	No Cannabis Session				Cannabis Session			
Blood Cannabinoid	Before	After	t-value	p	Before	After	t-value	p
THC	0.699 (1.540)	0.887 (1.685)	0.529	0.602	0.620 (1.029)	2.756* (2.112)	-4.401	< .001
11-OH-THC	0.284 (0.519)	0.284 (0.497)	1.469	0.157	0.205 (0.277)	2.361* (1.650)	-6.494	< .001
THC-COOH	16.655 (34.336)	13.135 (26.449)	1.538	0.139	8.700 (11.986)	23.645* (22.074)	-3.467	0.002
CBD	0.188 (0.210)	0.183 (0.187)	0.542	0.594	0.165 (0.183)	0.742 (1.337)	-2.051	0.053

3.5 Contrasts of the outcome measures between the Cannabis group and placebo group at 120min, 240min and 360min. (From Zhao et al. 2024)[22]

This excerpt and table were taken from the larger study (Zhao et al. 2024)[22] to describe the general findings of the changes in driving measures.

" Significant differences were observed for MS contrasting the least square means at 120 min between the Cannabis and the No Cannabis group under both single task (t(103.82) = -3.04, p = 0.003), which survived the correction for multiple comparisons (p = 0.027), and dual task conditions (t(103.88) = -2.38, p = 0.019), which did not survive the correction for multiple comparisons (p = 0.171). No significant effects on other driving measures were found; the number of collisions were too low to allow for analysis. " – Zhao et al.(2024)[22]

*Table 5: (Table taken from larger study (Zhao et al. 2024)[22]) "Descriptive means (SD) for driving outcomes under single-task conditions (upper table) and dual task conditions (middle table). Driving outcomes are presented for baseline as well as 120 min, 240 min and 360 min after ingesting cannabis (cannabis) or a control candy (no cannabis) condition. SDLP: standard deviation of lateral position (cm); MS: Mean Speed (km/hr); RT: Reaction time (seconds); SDSP: Standard deviation of speed; Max: maximum speed (km). Descriptive means (SD) of THC, OH-THC, COOH-THC and CBD (bottom table) at baseline and 120 min after cannabis or a control condition. *p<0.05, different from no cannabis for*

	Single task							
	No cannabis				Cannabis			
	Baseline	120	240	360	Baseline	120	240	360
SDLP	30.7 (6.1)	31.2 (6.9)	31.5 (6.4)	31.1 (6.5)	31.6 (7.4)	31.9 (6.9)	32.6 (7.9)	31.7 (7.0)
MS	82.2 (6.1)	82.6 (4.3)	82.2 (3.4)	82.3 (4.6)	81.6 (4.1)	**79.8 (4.8)***	82.3 (4.5)	81.9 (4.7)
SDSP	5.1 (2.4)	5.1 (2.5)	5.5 (2.8)	5.5 (2.5)	5.2 (2.5)	5.8 (2.7)	5.0 (2.0)	5.1 (1.9)
Max	95.2 (9.7)	95.3 (9.1)	96.6 (10.2)	95.2 (8.8)	93.7 (7.8)	92.8 (6.1)	95.4 (7.1)	95.0 (7.4)
RT	0.96 (0.11)	0.96 (0.10)	0.97 (0.11)	0.96 (0.10)	0.96 (0.13)	0.96 (0.13)	0.97 (0.10)	0.95 (0.09)

	Dual task							
	No cannabis				Cannabis			
	Baseline	120	240	360	Baseline	120	240	360
SDLP	28.3 (5.6)	28.4 (5.0)	29.3 (6.0)	29.3 (5.3)	28.9 (5.7)	30.3 (6.0)	30.4 (6.6)	29.4 (6.8)
MS	83.1 (6.6)	83.7 (6.2)	83.8 (6.0)	83.3 (5.5)	83.0 (5.1)	81.3 (4.4)+	83.3 (5.2)	83.9 (6.0)
SDSP	6.5 (4.0)	6.0 (2.4)	6.7 (3.5)	6.1 (2.5)	5.9 (2.1)	6.4 (2.5)	6.4 (2.6)	6.3 (2.6)
Max	99.2 (9.6)	99.7 (8.8)	100.9 (11.2)	99.8 (8.6)	100.4 (8.6)	98.4 (7.7)	101.4 (8.9)	100.0 (7.9)

	Blood							
	No cannabis				Cannabis			
	Baseline	120	240	360	Baseline	120	240	360
THC	0.70 (1.5)	0.90 (1.7)			0.6 (1.0)	**2.8 (2.1)***		
THC-COOH	16.7 (34.3)	13.1 (26.4)			8.7 (11.9)	**23.6 (22.1)***		
11-OH-THC	.29 (.52)	.28 (.50)			.21 (.28)	**2.4 (1.7)***		
CBD	.19 (.21)	.18 (.19)			.17 (.18)	**.74 (1.3)***		

3.6 The correlation between blood cannabinoid levels with driving outcomes in the cannabis group.

Correlation analysis between blood cannabinoid values at 120 minutes and driving measures reveled a significant negative correlation for the association between 11-OH-THC and Max Speed Single Task at 360 minutes after cannabis (Rs = -0.466, p = 0.029), suggesting that lower maximum speeds were associated with higher 11-OH-THC levels. The analysis also revealed significant negative correlation for the association between CBD levels and Mean Speed Dual Task at all times after cannabis (120 minutes: Rs = -0.48, p=0.024, 240 minutes: Rs = -0.597, p = 0.003, and 360 minutes: Rs = -0.439 , p = 0.041), suggesting that lower speed was associated with higher CBD levels. There were also significant correlations between CBD and measures of speed. A negative correlation was observed between CBD and SDSP Dual Task at 120 minutes: (Rs = -0.43, p = 0.046), suggesting lower variation in speed as blood CBD levels increased. A negative correlation was observed between CBD and Max Speed Dual Task at 240 minutes (Rs = -0.481, p = 0.023), suggesting that a decrease in maximal driving speeds were observed as blood CBD levels increased. This analysis did not reveal any other significant correlations between THC, metabolites of THC or CBD to any other driving measures.

Table 6. Correlations between blood cannabinoid levels at 120 minutes and SDLP at 120, 240 and 360 minutes. Top half represents SDLP Single Task, Bottom half represents SDLP Dual Task.

SDLP Single Task						
Blood	120 minutes		240 minutes		360 minutes	
	Rs	p	Rs	p	Rs	p
THC	-0.193	0.389	-0.147	0.512	-0.175	0.437
11-OH-THC	-0.294	0.184	-0.17	0.449	-0.141	0.532
THC-COOH	-0.214	0.339	-0.156	0.487	-0.147	0.513
CBD	-0.279	0.208	-0.294	0.184	-0.266	0.232
SDLP Dual Task						
Blood	120 minutes		240 minutes		360 minutes	
	Rs	p	Rs	p	Rs	p
THC	-0.111	0.622	-0.105	0.643	-0.085	0.706
11-OH-THC	-0.083	0.713	-0.148	0.511	-0.083	0.713
THC-COOH	-0.12	0.594	-0.097	0.669	-0.118	0.601
CBD	-0.293	0.186	-0.302	0.171	-0.353	0.107

Table 7. Correlations between blood cannabinoid levels at 120 minutes and Mean Speed at 120, 240 and 360 minutes. Top half represents Mean Speed Single Task, Bottom half represents Mean Speed Dual Task. Results in bold represent statistical significant results (p < 0.05).

Mean Speed Single Task						
	120 minutes		240 minutes		360 minutes	
Blood	Rs	p	Rs	p	Rs	p
THC	0.003	0.988	-0.081	0.721	0.218	0.331
11-OH-THC	-0.215	0.337	-0.027	0.905	-0.02	0.93
THC-COOH	0.024	0.915	-0.001	0.998	0.223	0.318
CBD	-0.099	0.661	-0.287	0.195	-0.109	0.631
Mean Speed Dual Task						
	120 minutes		240 minutes		360 minutes	
Blood	Rs	p	Rs	p	Rs	p
THC	0.017	0.94	-0.036	0.875	0.142	0.529
11-OH-THC	-0.149	0.509	-0.15	0.505	-0.121	0.592
THC-COOH	0.023	0.919	-0.047	0.836	0.181	0.42
CBD	**-0.48**	**0.024**	**-0.597**	**0.003**	**-0.439**	**0.041**

Table 8. Correlations between blood cannabinoid levels at 120 minutes and SDSP at 120, 240 and 360 minutes. Top half represents SDSP Single Task, Bottom half represents SDSP Dual Task. Results in bold represent statistical significant results (p < 0.05).

SDSP Single Task						
	120 minutes		240 minutes		360 minutes	
Blood	Rs	p	Rs	p	Rs	p
THC	0.088	0.696	-0.287	0.196	-0.345	0.116
11-OH-THC	0.208	0.353	-0.332	0.132	-0.308	0.163
THC-COOH	0.158	0.484	-0.093	0.68	-0.133	0.556
CBD	-0.023	0.921	-0.367	0.093	-0.175	0.435
SDSP Dual Task						
	120 minutes		240 minutes		360 minutes	
Blood	Rs	p	Rs	p	Rs	p
THC	-0.011	0.962	-0.142	0.527	-0.088	0.696
11-OH-THC	-0.102	0.651	-0.195	0.383	-0.141	0.532
THC-COOH	0.155	0.49	0.091	0.687	0.134	0.553
CBD	**-0.43**	**0.046**	-0.327	0.137	-0.247	0.269

Table 9. Correlations between blood cannabinoid levels at 120 minutes and Max Speed at 120, 240 and 360 minutes. Top half represents Max Speed Single Task, Bottom half represents Max Speed Dual Task. Results in bold represent statistical significant results ($p < 0.05$).

Max Speed Single Task						
	120 minutes		240 minutes		360 minutes	
Blood	Rs	p	Rs	p	Rs	p
THC	-0.074	0.743	-0.175	0.437	-0.384	0.078
11-OH-THC	-0.047	0.834	-0.093	0.68	**-0.466**	**0.029**
THC-COOH	-0.007	0.974	0.153	0.497	-0.217	0.331
CBD	-0.331	0.132	-0.175	0.435	-0.341	0.121
Max Speed Dual Task						
	120 minutes		240 minutes		360 minutes	
Blood	Rs	p	Rs	p	Rs	p
THC	0.099	0.66	-0.128	0.569	0.079	0.726
11-OH-THC	0.006	0.98	-0.243	0.276	-0.112	0.618
THC-COOH	0.104	0.644	-0.111	0.622	0.22	0.326
CBD	-0.293	0.186	**-0.481**	**0.023**	-0.402	0.064

Table 10. Correlations between blood cannabinoid levels at 120 minutes and Reaction Time at 120, 240 and 360 minutes.

Reaction Time						
	120 minutes		240 minutes		360 minutes	
Blood	Rs	p	Rs	p	Rs	p
THC	-0.198	0.376	-0.318	0.15	-0.031	0.893
11-OH-THC	-0.326	0.138	-0.328	0.136	0.093	0.68
THC-COOH	-0.317	0.151	-0.362	0.098	-0.019	0.934
CBD	-0.031	0.892	-0.322	0.144	-0.064	0.779

Figure 2: Graphical representation of association between Blood 11-OH-THC at 120 minutes after consumption and Max Speed for the Single Task Driving condition at 360 minutes after consumption. See Table 12.

11-OH-THC - Max Speed Single Task at 360 mins post-consumption

Rs = -0.466, p = 0.029

y-axis: km/hr

x-axis: Blood 11-OH-THC (ng/mL)
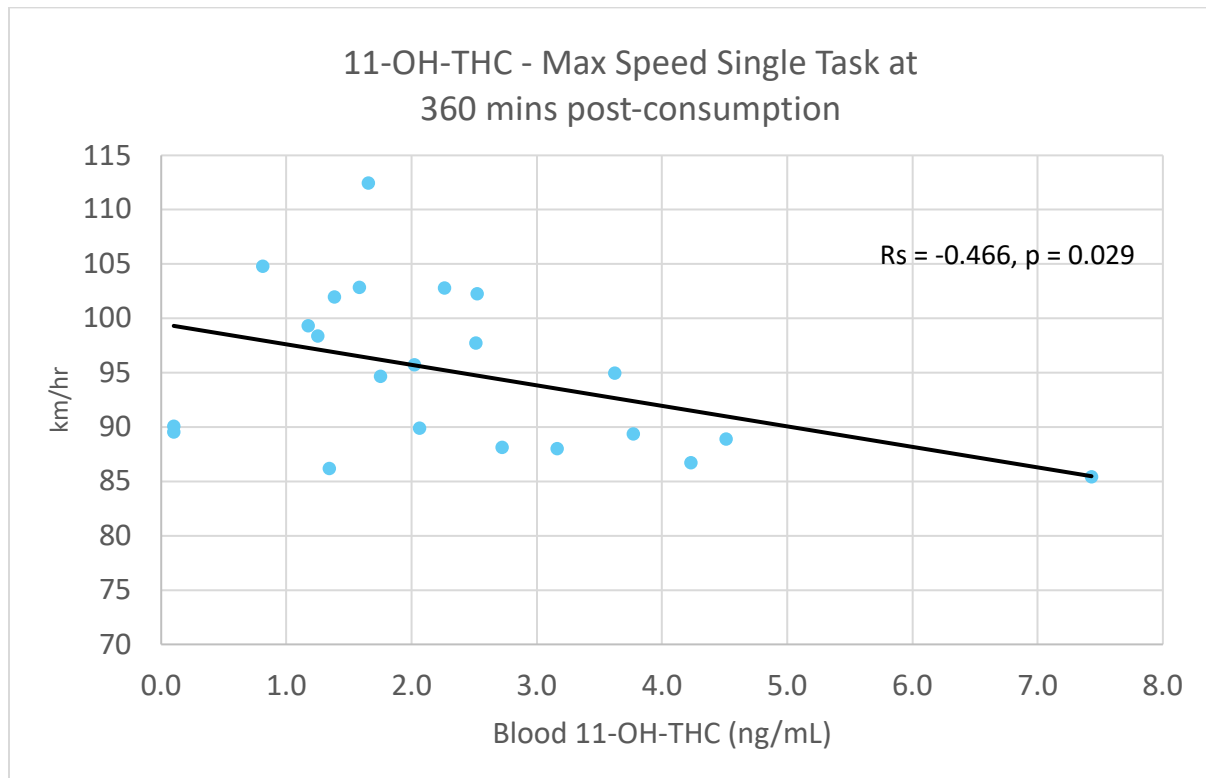
Figure 3: Graphical representation of association between Blood CBD at 120 minutes after consumption and Mean Speed for the Dual Task Driving Condition at 120, 240 and 360 minutes after consumption. See Table 10.

CBD - Mean Speed Dual Task at
120, 240, 360 mins post-consumption

120 min: Rs = -0.48, p = 0.024
240 min: Rs = -0.597, p = 0.003
360 min: Rs = -0.439, p = 0.041
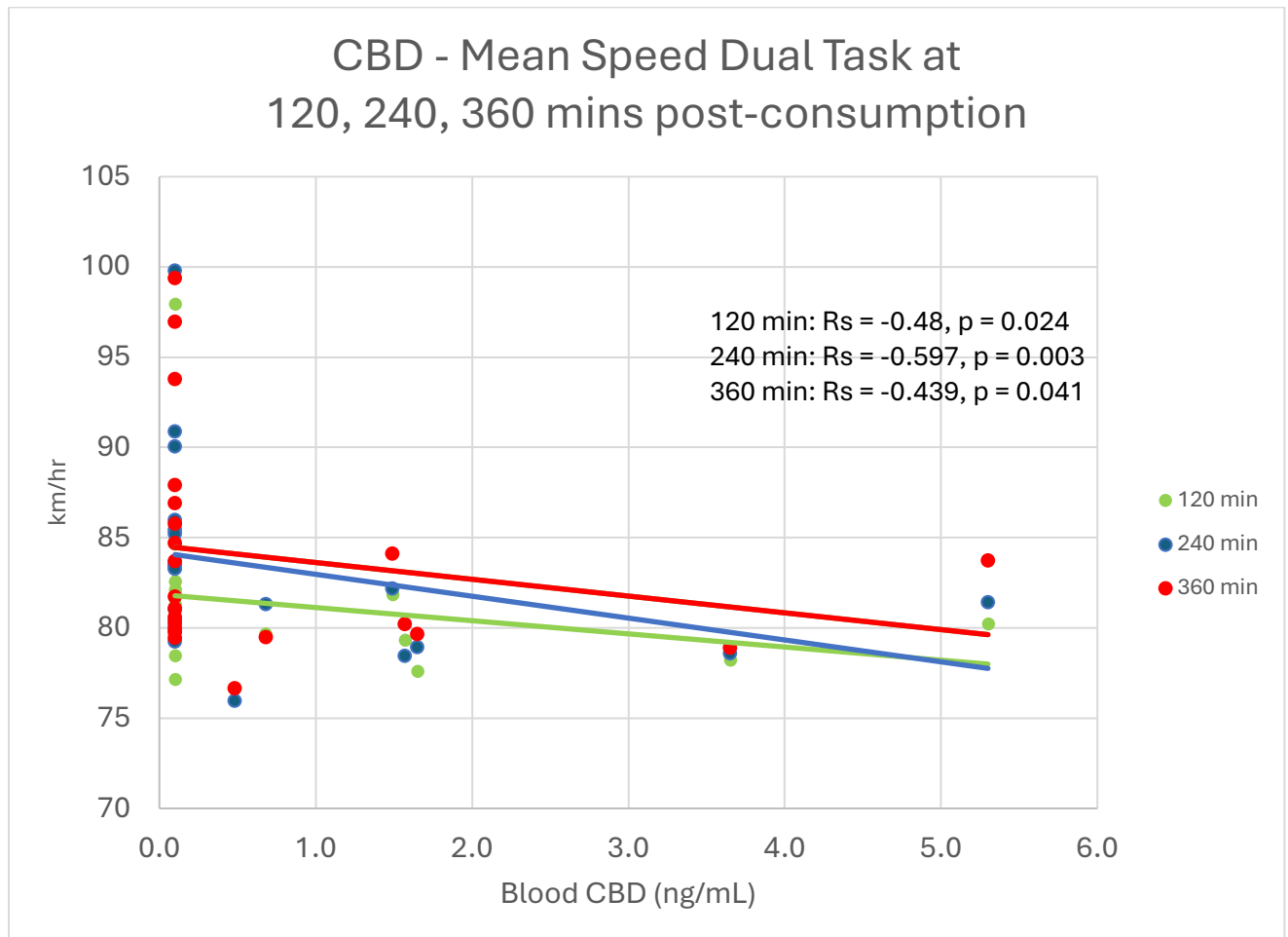
Figure 4: Graphical representation of association between Blood CBD at 120 minutes after consumption and SDSP for the Dual Task Driving Condition at 120 minutes after consumption. See Table 11.
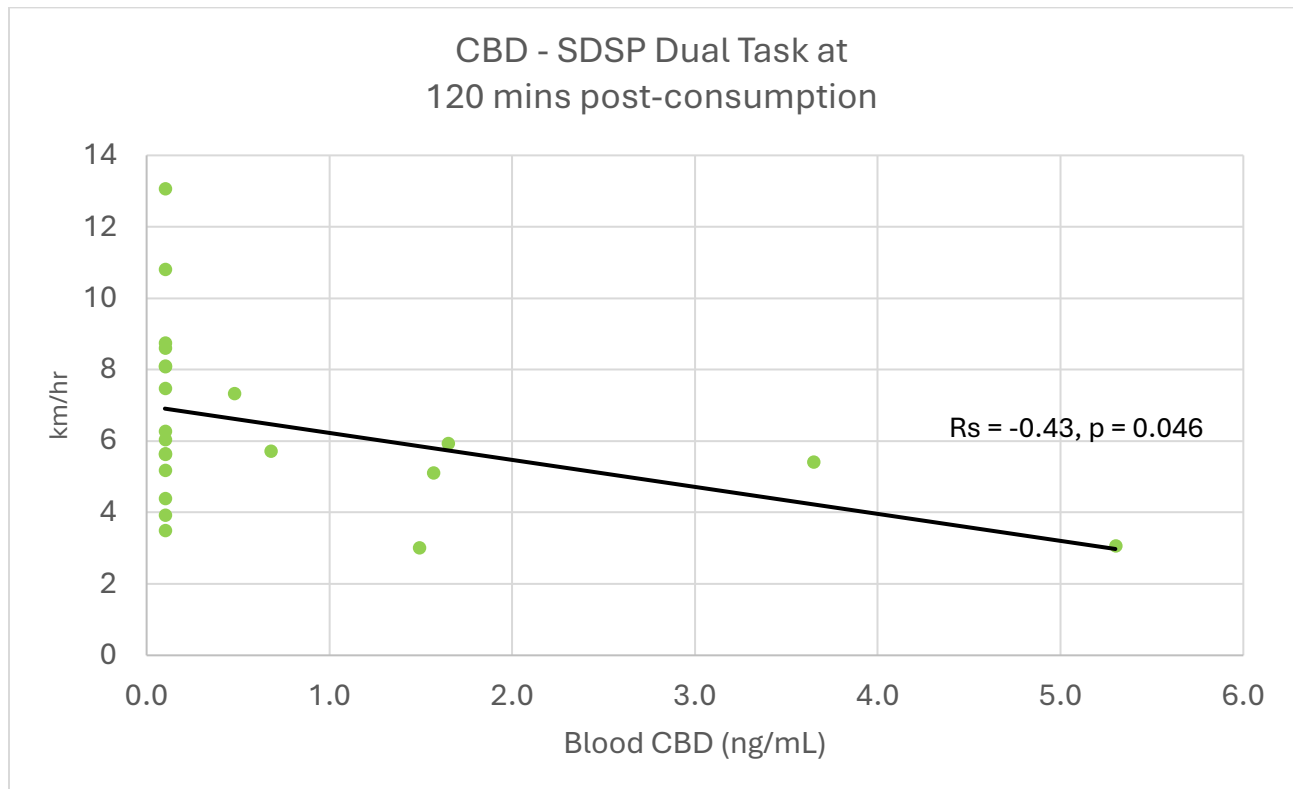
Figure 5: Graphical representation of association between Blood CBD at 120 minutes after consumption and Max Speed for the Dual Task Driving Condition at 240 minutes after consumption. See Table 11.

CBD - Max Speed Dual Task at 240 mins post-consumption

Rs = -0.481, p = 0.023
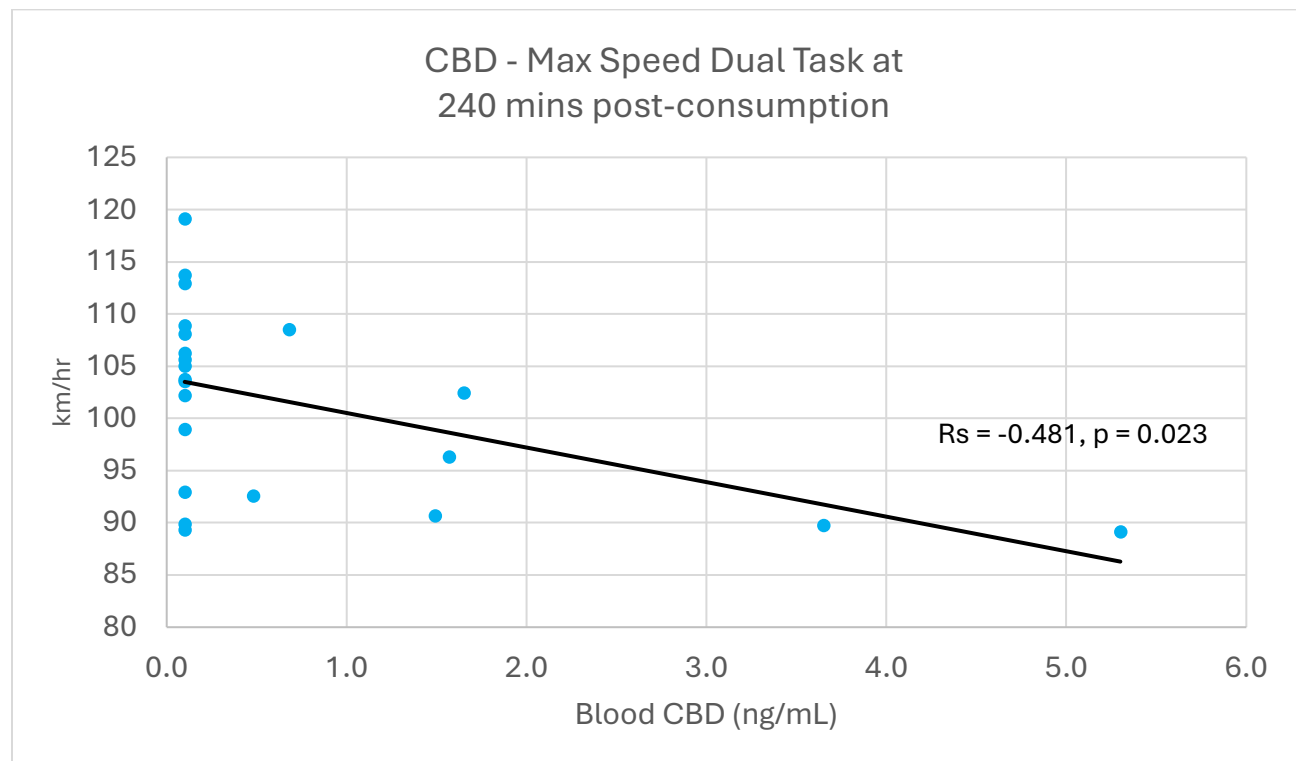
3.7   Testing the effectiveness of the 2ng/mL cut-off in detecting changes in driving measures

A within-subject comparison of the placebo to cannabis condition when they were either above or below the 2 ng/mL threshold revealed a significant difference in the Below group for Mean speed for both single and dual task driving measure at 120 minutes after consumption (single-task: $Z = -2.192$, $p = 0.028$, dual-task: $Z = -2.310$, $p = 0.021$) suggesting that mean speed is significantly affected by edible cannabis use when blood THC levels are below the threshold, but not above the threshold. The effect sizes were calculated using the Wilcoxon signed-rank test Z-value and revealed a 'medium' to 'large' effect size for multiple driving measures (See Table 11-15). All other driving revealed 'small' effect sizes. A between-subjects comparison was conducted using the Mann-Whitney U-test Z-value to compare the mean differences in the Above and Below 2ng/mL groups. This was followed by effect sizes. The test revealed 'medium' effect size for several driving measures at various time points, though none showed statistical significance (See Table 16-20). This analysis did not reveal any other significant changes between any other comparisons for any of the driving measures.

Table 11: Wilcoxon Signed-rank test comparing cannabis to placebo for SDLP at 120, 240 and 360 minutes. Participants were separated based on blood THC levels into above and below 2ng/mL groups. Top table represents SDLP Single Task, Bottom table represents SDLP Dual Task. Effect sizes were calculated through Wilcoxon signed-rank test. Bolded values represent 'medium' to 'large' effect size. * $p < 0.05$

SDLP Single Task									
Time after Treatment	Threshold	Placebo	SD	Drug	SD	n	Wilcoxon	p	Effect Size (r)
120 min	Above	29.582	6.881	31.967	8.283	13	-1.293	0.196	**0.359**
	Below	33.653	6.641	32.309	4.530	9	-0.770	0.441	0.257
240 min	Above	31.537	8.259	29.023	5.311	13	-1.013	0.311	0.281
	Below	32.489	5.518	33.426	7.655	9	-0.770	0.441	0.257
360 min	Above	30.788	7.013	31.031	7.383	13	-0.664	0.507	0.184
	Below	34.220	7.145	32.744	6.695	9	-1.007	0.314	**0.336**
SDLP Dual Task									
Time after Treatment	Threshold	Placebo	SD	Drug	SD	n	Wilcoxon	p	Effect Size (r)
120 min	Above	26.687	4.985	28.815	5.922	13	-1.572	0.116	**0.436**
	Below	30.921	4.179	32.430	5.724	9	-1.125	0.260	**0.375**
240 min	Above	29.162	6.203	30.946	8.028	13	-1.013	0.311	0.281
	Below	29.451	5.965	29.636	4.136	9	-0.415	0.678	0.138
360 min	Above	27.740	4.734	29.145	7.773	13	-0.664	0.507	0.184
	Below	31.438	5.518	29.865	5.427	9	-1.362	0.173	**0.454**

Table 13: Wilcoxon Signed-rank test comparing cannabis to placebo for Mean Speed at 120, 240 and 360 minutes. Participants were separated based on blood THC levels into above and below 2ng/mL groups. Top table represents Mean Speed Single Task, Bottom table represents Mean Speed Dual Task. Effect sizes were calculated through Wilcoxon signed-rank test. Bolded values represent 'medium' to 'large' effect size. * $p < 0.05$

Mean Speed Single Task									
Time after Treatment	Threshold	Placebo	SD	Drug	SD	n	Wilcoxon	p	Effect Size (r)
120 min	Above	81.186	2.535	80.597	4.720	13	-1.223	0.221	**0.339**
	Below	84.649	5.649	78.737	5.013	9	-2.192*	0.028	**0.731**
240 min	Above	81.221	2.287	81.999	5.304	13	-0.384	0.701	0.107
	Below	83.520	4.357	82.762	3.416	9	-0.533	0.594	0.178
360 min	Above	81.413	2.811	82.431	5.759	13	-0.454	0.650	0.126
	Below	83.592	6.278	81.180	2.755	9	-1.599	0.110	**0.533**
Mean Speed Dual Task									
Time after Treatment	Threshold	Placebo	SD	Drug	SD	n	Wilcoxon	p	Effect Size (r)
120 min	Above	81.991	5.259	81.819	5.355	13	-0.524	0.600	0.145
	Below	86.053	7.071	80.593	2.513	9	-2.310*	0.021	**0.770**
240 min	Above	82.132	5.120	83.050	5.810	13	-1.642	0.101	**0.455**
	Below	86.145	6.644	83.620	4.353	9	-1.481	0.139	**0.494**
360 min	Above	81.854	5.226	83.396	5.693	13	-1.642	0.101	**0.455**
	Below	85.344	5.412	84.539	6.695	9	-0.178	0.859	0.059

Table 13: Wilcoxon Signed-rank test comparing cannabis to placebo for SDSP at 120, 240 and 360 minutes. Participants were separated based on blood THC levels into above and below 2ng/mL groups. Top table represents SDSP Single Task, Bottom table represents SDSP Dual Task. Effect sizes were calculated through Wilcoxon signed-rank test. Bolded values represent 'medium' to 'large' effect size. * p < 0.05

SDSP Single Task									
Time after Treatment	Threshold	Placebo	SD	Drug	SD	n	Wilcoxon	p	Effect Size (r)
120 min	Above	4.535	2.183	6.244	3.139	13	-1.153	0.249	**0.320**
	Below	5.847	2.752	5.242	2.061	9	-1.125	0.260	**0.375**
240 min	Above	5.077	2.260	4.485	1.666	13	-1.223	0.221	**0.339**
	Below	6.220	3.515	5.704	2.409	9	-0.415	0.678	0.138
360 min	Above	5.220	2.550	4.589	1.721	13	-0.874	0.382	0.242
	Below	5.830	2.414	5.818	2.032	9	-0.178	0.859	0.059

SDSP Dual Task									
Time after Treatment	Threshold	Placebo	SD	Drug	SD	n	Wilcoxon	p	Effect Size (r)
120 min	Above	5.660	2.658	6.170	2.205	13	-1.293	0.196	**0.359**
	Below	6.587	1.861	6.788	2.935	9	-0.059	0.953	0.020
240 min	Above	5.939	3.546	6.425	2.940	13	-1.223	0.221	**0.339**
	Below	7.894	3.222	6.316	2.311	9	-1.244	0.214	**0.415**
360 min	Above	5.741	2.745	6.098	3.026	13	-0.594	0.552	0.165
	Below	6.694	2.023	6.575	1.877	9	-0.770	0.441	0.257

Table 14: Wilcoxon Signed-rank test comparing cannabis to placebo for Max Speed at 120, 240 and 360 minutes. Participants were separated based on blood THC levels into above and below 2ng/mL groups. Top table represents Max Speed Single Task, Bottom table represents Max Speed Dual Task. Effect sizes were calculated through Wilcoxon signed-rank test. Bolded values represent 'medium' to 'large' effect size. * p < 0.05

Max Speed Single Task									
Time after Treatment	Threshold	Placebo	SD	Drug	SD	n	Wilcoxon	p	Effect Size (r)
120 min	Above	92.573	7.010	92.520	6.396	13	-0.245	0.807	0.068
	Below	99.254	10.657	93.252	5.908	9	-1.718	0.086	**0.573**
240 min	Above	94.323	8.118	94.007	5.764	13	-0.035	0.972	0.010
	Below	99.972	12.411	97.456	8.632	9	-0.059	0.953	0.020
360 min	Above	93.052	6.645	93.262	7.337	13	-0.384	0.701	0.107
	Below	98.333	10.911	97.615	7.064	9	-0.059	0.953	0.020
Max Speed Dual Task									
Time after Treatment	Threshold	Placebo	SD	Drug	SD	n	Wilcoxon	p	Effect Size (r)
120 min	Above	96.830	7.635	99.067	8.686	13	-0.804	0.422	0.223
	Below	103.908	9.113	97.512	6.399	9	-1.955	0.051	**0.652**
240 min	Above	97.375	9.841	100.936	9.335	13	-0.734	0.463	0.204
	Below	105.929	11.702	102.001	8.830	9	-0.652	0.515	0.217
360 min	Above	97.379	6.920	99.642	7.775	13	-1.572	0.116	**0.436**
	Below	103.189	10.004	100.590	8.428	9	-1.125	0.260	**0.375**

Table 15: Wilcoxon Signed-rank test comparing cannabis to placebo for Reaction Time at 120, 240 and 360 minutes. Participants were separated based on blood THC levels into above and below 2ng/mL groups. Effect sizes were calculated through Wilcoxon signed-rank test. Bolded values represent 'medium' to 'large' effect size. * p < 0.05

Reaction Time									
Time after Treatment	Threshold	Placebo	SD	Drug	SD	n	Wilcoxon	p	Effect Size (r)
120 min	Above	0.940	0.090	0.953	0.132	13	-0.524	0.600	0.145
	Below	0.997	0.120	0.976	0.145	9	-0.652	0.515	0.217
240 min	Above	0.949	0.102	0.941	0.096	13	-0.035	0.972	0.010
	Below	1.005	0.120	1.009	0.104	9	-0.415	0.678	0.138
360 min	Above	0.914	0.062	0.927	0.083	13	-0.314	0.753	0.087
	Below	1.015	0.125	0.980	0.091	9	-1.007	0.314	**0.336**

Table 16: Mann-Whitney U-Test Effect size calculations for comparing the differences between the Above and Below 2ng/mL Threshold Groups (Placebo-Cannabis Conditions) for SDLP at 120, 240 and 360 minutes. Bolded values represent 'medium' to 'large' effect size.

SDLP Single Task									
Time after Treatment	Above	SD	N	Below	SD	N	Z (Mann Whitney)	p-value	Effect Size (r)
120 minutes	1.955	3.902	13	-1.344	4.727	9	-1.369	0.171	**0.350**
240 minutes	1.179	4.318	13	0.936	2.802	9	-0.301	0.764	0.077
360 minutes	2.008	7.588	13	-1.475	4.361	9	-1.235	0.217	**0.316**
SDLP Dual Task									
Time after Treatment	Above	SD	N	Below	SD	N	Z (Mann Whitney)	p-value	Effect Size (r)
120 minutes	2.128	4.137	13	1.509	3.446	9	-0.568	0.57	0.145
240 minutes	1.783	5.391	13	0.185	3.866	9	-0.902	0.367	0.231
360 minutes	1.405	4.142	13	-1.573	3.135	9	-1.302	0.193	**0.333**

Table 17: Mann-Whitney U-Test Effect size calculations for comparing the differences between the Above and Below 2ng/mL Threshold Groups (Placebo-Cannabis Conditions) for Mean Speed at 120, 240 and 360 minutes. Bolded values represent 'medium' to 'large' effect size.

Mean Speed Single Task									
Time after Treatment	Above	SD	N	Below	SD	N	Z (Mann Whitney)	p-value	Effect Size (r)
120 minutes	0.590	3.311	13	5.912	8.661	9	-1.302	0.193	**0.333**
240 minutes	-0.778	4.229	13	0.758	3.328	9	-0.568	0.57	0.145
360 minutes	-1.018	4.022	13	2.412	5.062	9	-1.636	0.102	**0.419**
Mean Speed Dual Task									
Time after Treatment	Above	SD	N	Below	SD	N	Z (Mann Whitney)	p-value	Effect Size (r)
120 minutes	0.172	6.723	13	5.460	7.432	9	-1.903	0.057	**0.487**
240 minutes	-0.918	5.184	13	2.524	4.650	9	-1.836	0.066	**0.470**
360 minutes	-1.542	4.825	13	0.805	5.123	9	-0.835	0.404	0.214

Table 18: Mann-Whitney U-Test Effect size calculations for comparing the differences between the Above and Below 2ng/mL Threshold Groups (Placebo-Cannabis Conditions) for SDSP at 120, 240 and 360 minutes. Bolded values represent 'medium' to 'large' effect size.

SDSP Single Task									
Time after Treatment	Above	SD	N	Below	SD	N	Z (Mann Whitney)	p-value	Effect Size (r)
120 minutes	1.709	3.797	13	-0.605	1.571	9	-1.503	0.133	**0.385**
240 minutes	-0.592	1.436	13	-0.517	2.339	9	-0.167	0.867	0.043
360 minutes	-0.631	1.714	13	-0.012	1.589	9	-0.768	0.443	0.197
SDSP Dual Task									
Time after Treatment	Above	SD	N	Below	SD	N	Z (Mann Whitney)	p-value	Effect Size (r)
120 minutes	0.511	1.545	13	0.201	2.722	9	-0.501	0.616	0.128
240 minutes	0.486	1.746	13	-1.578	3.014	9	-1.703	0.089	**0.436**
360 minutes	0.357	1.344	13	-0.119	1.411	9	-0.701	0.483	0.179

Table 19: Mann-Whitney U-Test Effect size calculations for comparing the differences between the Above and Below 2ng/mL Threshold Groups (Placebo-Cannabis Conditions) for Max Speed at 120, 240 and 360 minutes. Bolded values represent 'medium' to 'large' effect size.

Max Speed Single Task									
Time after Treatment	Above	SD	N	Below	SD	N	Z (Mann Whitney)	p-value	Effect Size (r)
120 minutes	-0.053	5.250	13	-6.002	9.303	9	-1.503	0.133	**0.385**
240 minutes	-0.316	6.686	13	-2.516	8.388	9	-0.301	0.764	0.077
360 minutes	0.210	3.487	13	-0.718	8.353	9	-0.167	0.867	0.043
Max Speed Dual Task									
Time after Treatment	Above	SD	N	Below	SD	N	Z (Mann Whitney)	p-value	Effect Size (r)
120 minutes	2.237	11.525	13	-6.395	8.289	9	-1.703	0.089	**0.436**
240 minutes	3.561	8.767	13	-3.928	10.182	9	-1.703	0.089	**0.436**
360 minutes	2.263	7.680	13	-2.599	7.605	9	-1.369	0.171	**0.350**

Table 20: Mann-Whitney U-Test Effect size calculations for comparing the differences

between the Above and Below 2ng/mL Threshold Groups (Placebo-Cannabis Conditions)

for Reaction Time at 120, 240 and 360 minutes. Bolded values represent 'medium' to

'large' effect size.

Reaction Time									
Time after Treatment	Above	SD	N	Below	SD	N	Z (Mann Whitney)	p-value	Effect Size (r)
120 minutes	0.023	0.136	13	-0.036	0.082	9	-0.568	0.57	0.145
240 minutes	-0.008	0.082	13	0.005	0.086	9	-0.033	0.973	0.009
360 minutes	-0.009	0.093	13	-0.004	0.088	9	-0.234	0.815	0.060

3.8   Investigating the median blood THC concentration as a cut-off

A within-subject comparison of the placebo to cannabis condition when they were either above or below the median threshold revealed a significant difference in the Below group when looking at Mean speed for both single and dual task driving measures at 120 minutes after consumption (Single Task : Z = -2.045, p = 0.041, Dual Task: Z = -2.045, p = 0.041), suggesting that for both driving conditions, a significant decrease in mean speed was observed in the below median group, but not in the above median group. The effect sizes were calculated using the Wilcoxon signed-rank test Z-value and revealed a 'medium' to 'large' effect size for multiple driving measures (See Table 21-25). All other driving measures revealed 'small' effect sizes. A between-subjects comparison was conducted to compare differences between the Above and Below median groups (placebo-cannabis condition) and revealed 'medium' to 'large' effect size for multiple driving measures, at various time points (See Table 26-30). Mean and maximum speed in the dual task driving condition at 240 minutes post-consumption revealed a 'large' effect size and were statistically significant (p < 0.05). All other driving measures revealed 'small' effect sizes. This analysis did not reveal any other significant changes between the placebo and drug conditions for any of the driving measures.

Table 22: Wilcoxon signed-rank test comparing cannabis to placebo for SDLP at 120, 240 and 360 minutes. Participants were separated based on blood THC levels into above and below median groups. Top table represents SDLP Single Task, Bottom table represents SDLP Dual Task. Effect sizes were calculated through Wilcoxon Z-value. Bolded values represent 'medium' to 'large' effect size.

SDLP Single Task									
Time after Treatment	Threshold	Placebo	SD	Drug	SD	n	Wilcoxon	p	Effect Size (r)
120 min	Above	30.246	7.324	31.928	8.763	11	-0.445	0.657	0.128
	Below	32.248	6.713	31.777	4.668	11	-1.067	0.286	**0.308**
240 min	Above	30.922	7.531	32.642	8.448	11	-0.356	0.722	0.103
	Below	32.045	5.245	32.485	7.679	11	-1.334	0.182	**0.385**
360 min	Above	29.356	5.429	31.416	7.606	11	-0.533	0.594	0.154
	Below	32.941	7.246	32.048	6.690	11	-0.356	0.722	0.103
SDLP Dual Task									
Time after Treatment	Threshold	Placebo	SD	Drug	SD	n	Wilcoxon	p	Effect Size (r)
120 min	Above	26.672	5.461	28.901	5.833	11	-1.067	0.286	**0.308**
	Below	30.167	4.097	31.687	6.079	11	-1.867	0.062	**0.539**
240 min	Above	29.699	6.577	31.270	8.728	11	-0.889	0.374	0.257
	Below	28.862	5.572	29.550	3.757	11	-0.711	0.477	0.205
360 min	Above	27.898	4.907	29.282	8.034	11	-1.156	0.248	**0.334**
	Below	30.607	5.515	29.597	5.634	11	-0.445	0.657	0.128

Table 23: Wilcoxon signed-rank test comparing cannabis to placebo for Mean Speed at 120, 240 and 360 minutes. Participants were separated based on blood THC levels into above and below median groups. Top table represents Mean Speed Single Task, Bottom table represents Mean Speed Dual Task. Effect sizes were calculated through Wilcoxon Z-value. Bolded values represent 'medium' to 'large' effect size.

Mean Speed Single Task									
Time after Treatment	Threshold	Placebo	SD	Drug	SD	n	Wilcoxon	p	Effect Size (r)
120 min	Above	81.569	2.450	80.939	5.081	11	-1.245	0.213	**0.389**
	Below	**83.637**	**5.591**	**78.733**	**4.493**	11	**-2.045**	**0.041**	**0.502**
240 min	Above	81.106	2.415	82.117	5.645	11	-0.445	0.657	0.010
	Below	83.217	3.999	82.504	3.384	11	-0.622	0.534	0.104
360 min	Above	81.615	3.032	82.547	6.294	11	0.000	1.000	0.104
	Below	82.994	5.771	81.292	2.493	11	-0.978	0.328	0.161
Mean Speed Dual Task									
Time after Treatment	Threshold	Placebo	SD	Drug	SD	n	Wilcoxon	p	Effect Size (r)
120 min	Above	82.431	5.630	82.013	5.809	11	-0.711	0.477	0.205
	Below	**84.875**	**6.854**	**80.621**	**2.334**	11	**-2.045**	**0.041**	**0.590**
240 min	Above	82.342	5.533	83.444	6.183	11	-1.689	0.091	**0.488**
	Below	85.205	6.341	83.123	4.189	11	-1.511	0.131	**0.436**
360 min	Above	81.979	5.699	83.656	6.148	11	-1.423	0.155	**0.411**
	Below	84.585	5.145	84.071	6.128	11	-0.089	0.929	0.026

Table 24: Wilcoxon signed-rank test comparing cannabis to placebo for SDSP at 120, 240 and 360 minutes. Participants were separated based on blood THC levels into above and below median groups. Top table represents SDSP Single Task, Bottom table represents SDSP Dual Task. Effect sizes were calculated through Wilcoxon Z-value. Bolded values represent 'medium' to 'large' effect size.

SDSP Single Task									
Time after Treatment	Threshold	Placebo	SD	Drug	SD	n	Wilcoxon	p	Effect Size (r)
120 min	Above	4.588	2.382	6.621	3.267	11	-1.245	0.213	**0.359**
	Below	5.557	2.550	5.048	1.928	11	-1.156	0.248	**0.334**
240 min	Above	5.208	2.389	4.460	1.810	11	-1.600	0.110	**0.462**
	Below	5.882	3.279	5.508	2.210	11	-0.267	0.790	0.077
360 min	Above	5.369	2.762	4.464	1.845	11	-1.600	0.110	**0.462**
	Below	5.571	2.239	5.720	1.841	11	-0.711	0.477	0.205
SDSP Dual Task									
Time after Treatment	Threshold	Placebo	SD	Drug	SD	n	Wilcoxon	p	Effect Size (r)
120 min	Above	5.750	2.901	6.313	2.382	11	-1.156	0.248	**0.334**
	Below	6.328	1.763	6.533	2.688	11	-0.356	0.722	0.103
240 min	Above	5.913	3.884	6.373	3.218	11	-0.889	0.374	0.257
	Below	7.565	2.973	6.388	2.074	11	-0.711	0.477	0.205
360 min	Above	5.747	2.985	6.175	3.307	11	-0.800	0.424	0.231
	Below	6.515	1.889	6.410	1.720	11	-0.622	0.534	0.180

Table 25: Wilcoxon Signed-rank test comparing cannabis to placebo for Max Speed at 120, 240 and 360 minutes. Participants were separated based on blood THC levels into above and below median groups. Top table represents Max speed Single Task, Bottom table represents Max speed Dual Task. Effect sizes were calculated through Wilcoxon Z-value. Bolded values represent 'medium' to 'large' effect size.

MAX speed Single Task									
Time after Treatment	Threshold	Placebo	SD	Drug	SD	n	Wilcoxon	p	Effect Size (r)
120 min	Above	93.113	7.403	93.331	6.659	11	-0.533	0.594	0.154
	Below	97.500	10.400	92.308	5.691	11	-1.778	0.075	**0.513**
240 min	Above	94.765	8.635	93.954	6.312	11	-0.178	0.859	0.051
	Below	98.503	11.706	96.883	7.826	11	0.000	1.000	0.000
360 min	Above	93.246	7.232	92.664	7.833	11	-0.445	0.657	0.128
	Below	97.179	10.112	97.422	6.387	11	-0.445	0.657	0.128
MAX speed Dual Task									
Time after Treatment	Threshold	Placebo	SD	Drug	SD	n	Wilcoxon	p	Effect Size (r)
120 min	Above	98.113	7.591	99.427	9.305	11	-0.267	0.790	0.077
	Below	101.337	9.985	97.435	5.985	11	-1.334	0.182	**0.385**
240 min	Above	96.314	10.216	100.700	9.864	11	-1.511	0.131	**0.436**
	Below	105.436	10.703	102.044	8.322	11	-0.711	0.477	0.205
360 min	Above	96.613	7.227	99.846	8.470	11	-1.778	0.075	**0.513**
	Below	102.899	9.028	100.214	7.618	11	-1.245	0.213	**0.359**

Table 26: Wilcoxon Signed-rank test comparing cannabis to placebo for Reaction time at 120, 240 and 360 minutes. Participants were separated based on blood THC levels into above and below 2ng/mL groups. Effect sizes were calculated through Wilcoxon Z-value. Bolded values represent 'medium' to 'large' effect size.

Reaction time									
Time after Treatment	Threshold	Placebo	SD	Drug	SD	n	Wilcoxon	p	Effect Size (r)
120 min	Above	0.933	0.070	0.930	0.129	11	-0.800	0.424	0.231
	Below	0.994	0.127	0.995	0.137	11	-0.445	0.657	0.128
240 min	Above	0.924	0.062	0.931	0.097	11	-0.533	0.594	0.154
	Below	1.020	0.130	1.007	0.098	11	-0.267	0.790	0.077
360 min	Above	0.903	0.055	0.929	0.091	11	-0.800	0.424	0.231
	Below	1.008	0.116	0.969	0.085	11	-1.423	0.155	**0.411**

Table 27: Mann-Whitney U-test Effect size calculations comparing the differences between the Above and Below Median Threshold Groups (Placebo-Cannabis Conditions) for SDLP at 120, 240 and 360 minutes. Bolded values represent 'medium' to 'large' effect size.

SDLP Single Task									
Time after Treatment	Above	SD	N	Below	SD	N	Z (Mann Whitney)	p-value	Effect Size (r)
120 minutes	1.682	3.660	11	-0.471	5.098	11	-1.083	0.279	0.273
240 minutes	1.719	4.313	11	0.440	3.031	11	-1.018	0.309	0.256
360 minutes	2.060	8.285	11	-0.894	4.162	11	-0.821	0.412	0.207
SDLP Dual Task									
Time after Treatment	Above	SD	N	Below	SD	N	Z (Mann Whitney)	p-value	Effect Size (r)
120 minutes	2.230	3.544	11	1.520	4.172	11	-0.624	0.533	0.157
240 minutes	1.571	5.871	11	0.688	3.647	11	-0.295	0.768	0.074
360 minutes	1.384	4.383	11	-1.010	3.287	11	-0.821	0.412	0.207

Table 28: Mann-Whitney U-test Effect size calculations comparing the differences between the Above and Below Median Threshold Groups (Placebo-Cannabis Conditions) for Mean Speed at 120, 240 and 360 minutes. Bolded values represent 'medium' to 'large' effect size. * p<0.05

Mean Speed Single Task									
Time after Treatment	Above	SD	N	Below	SD	N	Z (Mann Whitney)	p-value	Effect Size (r)
120 minutes	0.630	3.457	11	4.904	8.139	11	-0.886	0.375	0.207
240 minutes	-1.011	4.165	11	0.712	3.549	11	-0.558	0.577	0.074
360 minutes	-0.932	4.391	11	1.702	4.804	11	-0.755	0.45	0.190
Mean Speed Dual Task									
Time after Treatment	Above	SD	N	Below	SD	N	Z (Mann Whitney)	p-value	Effect Size (r)
120 minutes	0.418	7.274	11	4.254	7.232	11	-1.280	0.200	0.289
240 minutes	-1.102	5.646	11	2.082	4.289	11	-2.003*	0.045	**0.355**
360 minutes	-1.677	5.262	11	0.513	4.642	11	-0.821	0.412	0.091

Table 29: Mann-Whitney U-test Effect size calculations comparing the differences between the Above and Below Median Threshold Groups (Placebo-Cannabis Conditions) for SDSP at 120, 240 and 360 minutes. Bolded values represent 'medium' to 'large' effect size.

SDSP Single Task									
Time after Treatment	Above	SD	N	Below	SD	N	Z (Mann Whitney)	p-value	Effect Size (r)
120 minutes	2.033	4.063	11	-0.509	1.435	11	-1.609	0.108	**0.405**
240 minutes	-0.749	1.482	11	-0.374	2.140	11	-0.755	0.450	0.190
360 minutes	-0.905	1.728	11	0.150	1.467	11	-1.543	0.123	**0.388**
SDSP Dual Task									
Time after Treatment	Above	SD	N	Below	SD	N	Z (Mann Whitney)	p-value	Effect Size (r)
120 minutes	0.563	1.686	11	0.205	2.435	11	-0.624	0.533	0.157
240 minutes	0.461	1.911	11	-1.177	2.840	11	-1.280	0.200	**0.322**
360 minutes	0.428	1.432	11	-0.104	1.294	11	-0.689	0.491	0.174

Table 30: Mann-Whitney U-test Effect size calculations comparing the differences between the Above and Below Median Threshold Groups (Placebo-Cannabis Conditions) for Max Speed at 120, 240 and 360 minutes. Bolded values represent 'medium' to 'large' effect size. *p<0.05

Max Speed Single Task									
Time after Treatment	Above	SD	N	Below	SD	N	Z (Mann Whitney)	p-value	Effect Size (r)
120 minutes	0.218	5.452	11	-5.191	8.678	11	-1.609	0.108	**0.405**
240 minutes	-0.811	6.974	11	-1.621	7.969	11	-0.033	0.974	0.008
360 minutes	-0.582	3.173	11	0.243	7.773	11	-1.149	0.250	0.289
Max Speed Dual Task									
Time after Treatment	Above	SD	N	Below	SD	N	Z (Mann Whitney)	p-value	Effect Size (r)
120 minutes	1.313	12.128	11	-3.902	9.587	11	-0.886	0.375	0.223
240 minutes	4.387	9.322	11	-3.392	9.209	11	-2.134*	0.033	**0.537**
360 minutes	3.233	7.813	11	-2.685	7.023	11	-1.806	0.071	**0.455**

Table 31: Mann-Whitney Effect size calculations comparing the differences between the Above and Below Median Threshold Groups (Placebo-Cannabis Conditions) for Reaction Time at 120, 240 and 360 minutes. Bolded values represent 'medium' to 'large' effect size.

Reaction Time									
Time after Treatment	Above	SD	N	Below	SD	N	Z (Mann Whitney)	p-value	Effect Size (r)
120 minutes	-0.004	0.122	11	0.001	0.120	11	-0.361	0.718	0.091
240 minutes	0.007	0.083	11	-0.013	0.084	11	-0.624	0.533	0.157
360 minutes	0.025	0.089	11	-0.039	0.081	11	-1.839	0.066	**0.463**

4   Discussion

The main finding of the study conducted by Zhao et al. (2024)[122] was a significant decrease in mean speed 2 hours after cannabis edible consumption, with no notable changes observed at the 4 and 6-hour marks. Other driving measures remained unaffected by the consumption of edible cannabis at all observed time points. Blood levels of THC, its metabolites, and CBD increased 2 hours after consumption.

This secondary analysis had found a negative correlation was identified between blood levels of 11-OH-THC and the maximum speed during the single-task driving condition at 6 hours post-consumption. Blood CBD levels were negatively correlated with mean speed, SDSP, and maximum speed at various time points in the dual task driving condition, but not the single task condition. A significant decrease in mean speed was observed after cannabis in the below 2ng/mL threshold group, but no significant changes were observed in the above 2ng/mL threshold group. Additionally, a significant decrease in mean speed was seen in the below median (2.3 ng/mL) threshold group, but not in the above median threshold group. Effect size calculations comparing placebo and cannabis conditions either above or below the thresholds showed 'medium' to 'large' effect sizes for most driving measures. Effect size calculations for comparing the mean difference (cannabis-placebo) for the above and below threshold groups indicated a 'medium' to 'large' effect size for multiple driving measures.

4.1　Findings of the Parent Paper

The findings had revealed that edible cannabis causes a decrease in mean speed, specifically 120 minutes after consumption, but not at 240 and 360 minutes. Other driving measures did not show significant changes. This is as expected, as there is a growing body of literature observing a decrease in mean speed in studies examining the effects of smoked and vaped cannabis on driving, indicating that mean speed is a sensitive driving measure of cannabis use[14,15,20,22-25,121]. As described in the review by Neavyn et al., decreases in speed are often associated with attempts to compensate for the subjective effects of cannabis intoxication, such as lapses in attention[67]. However, there is some literature indicating the opposite, where these studies have reported no significant decrease in mean speed following cannabis consumption[121,123]. For instance, Manning et al. observed an increase in mean speed 2.5 and 5 hours after consuming oral cannabis products, particularly in participants using oil-based medical cannabis[124]. The authors of this study attributed the increase in speed with increased tolerance and increased familiarity with the cannabis product due to the chronic nature of medical cannabis use, resulting to a milder level of intoxication, and thus, less caution associated with the subjective effects associated with cannabis use[124]. While tolerance may affect the interpretation of the various outcome measures, overall, the findings show that the consumption of cannabis edibles led to the decrease in mean speed.

No significant changes were observed at any time point after consumption for any of the driving measures except for mean speed. There is existing literature supporting the

lack of significant findings, like Ogourtsova et al., where they had reported similar findings, as no significant changes were observed in SDLP and braking after the consumption of 100mg of vaporized cannabis[17]. There is a larger body of studies that have found that driving measures like SDLP[4,10-22] and reaction time[13,14,26,108] are sensitive to the effects of cannabis. For instance, a recent study by Di Ciano et al. found that SDLP significantly increased by 2cm after smoked cannabis consumption[120]. A review by Alvarez et al. has reported that reaction time decreased in THC conditions in multiple studies investigating the effects of cannabis in young adults[13,14,26,108]. It was hypothesized that the non-significant findings for other driving measures might result from the low THC dose (7.3 mg of THC) in edible cannabis and the limited understanding of its effects on driving, suggesting that edible cannabis might affect driving differently than smoked or vaped cannabis. The sensitivity of the driving simulator was also questioned, as it may not have been adequate to detect changes in driving measures given the low THC and CBD doses. As this was one of the first studies investigating the effects of edible cannabis on simulated driving, further exploration around the understanding how these factors may play a role in affecting intoxication is needed.

Blood THC, THC metabolites, and CBD levels increased 2 hours after cannabis consumption, aligning with the hypothesis. Mean blood THC increases were lower than those observed in smoked and vaped cannabis studies[86,87,111], which can be attributed to the significantly different aspects of cannabis absorption between smoked, vaped and edible cannabis[86]. Primarily, when comparing pharmacokinetics of THC between smoked and edible cannabis, higher plasma concentrations of THC were achieved significantly

faster when participants consume smoked cannabis, in comparison to edible cannabis[125].

Edible cannabis undergoes absorption through the GI system, resulting in THC interacting

with various metabolism pathways, such as first-pass metabolism, resulting in lower

bioavailability of THC in the plasma[84]. In contrast, smoked cannabis delivers THC directly

to the bloodstream via the lungs, bypassing first-pass metabolism and resulting in higher

bioavailability of THC in the plasma[83]. As there are inter-personal variability that could

affect the pharmacokinetics of cannabis, which include differences in absorption of THC

and CBD from the GI tract to circulation[126], hepatic cytochrome P450 protein expression,

as well as other factors, this may result in the high level of variability in blood THC

concentration observed in this study. These factors similarly explain the observed blood

THC metabolite and CBD levels. Overall, edible cannabis consumption resulted in a

significant increase in blood cannabinoid levels.

4.2   The correlation between blood cannabinoid levels with driving outcomes in the cannabis Condition.

The analysis of the blood cannabinoid levels and driving measures revealed no

significant correlation between blood THC, THC metabolites, and most driving measures,

for both single and dual-task driving conditions, except for a correlation that was found

between blood 11-OH-THC and maximum driving speed during the single-task driving

condition at 360 minutes after cannabis consumption. This suggests that an increase in

blood 11-OH-THC levels is associated with a decrease in maximum speed at this time

point. The current results show a novel significant correlation that was never previously reported in the literature.

The current relationship between blood cannabinoid levels and changes in driving is an ongoing topic of research in this field, as previous studies have explored correlations between blood cannabinoid levels and changes in driving measures, albeit with mixed results. For instance, Hartman et al. reported a regression model that predicted significant correlations between increases in blood THC levels and decreases in mean speed, as well as increases in time spent at lower speeds[25]. A similar analysis by the same group found a significant correlation between increases in blood THC and increases in SDLP, where blood THC increased SDLP by 0.26 cm per μg/L blood THC[34]. Despite these supporting publications, most current literature concludes that there are no linear correlations between blood THC and various driving measures[15,19,22,23,27,29-31] and overall driving performance[32,33]. The current literature has focused on investigating correlations using blood THC, and not other cannabinoids. Future studies should include analyses of other blood cannabinoids to validate the novel discovery found in this analysis.

The correlation reported in this analysis between blood 11-OH-THC levels and maximum speed may represent the effects of THC. 11-OH-THC is one of the major metabolites formed from the metabolism of THC that can easily cross the blood brain barrier, and shares similar psychotropic effects and pharmacological targets to THC . In addition, it has been found to affect cognitive domains including executive function, information processing, visuomotor coordination and other cognitive functions, which are all required in the complex task of driving[68,69]. Specifically, correlations have been

observed between blood 11-OH-THC levels and changes in driving-related cognitive function, though the findings are inconsistent[10,86,127]. In a review by McCartney et al., they reviewed several studies that found no significant correlations between blood 11-OH-THC and Digit Symbol Substitution Task (DSST), the Divided attention task (DAT) and the Paced Serial Addition Test (PASAT)[86,128], though a study done by Schlienz et al. showed significant correlations between blood 11-OH-THC to DAT and PASAT scores after consumption of oral cannabis[129]. Though the current results show that blood THC does not have any direct relationships to changes in driving measures, the negative correlation between 11-OH-THC and maximum speed do suggest that metabolites of THC may act as a better proxy for measurements and correlations. Overall, the current findings are novel in that no previous literature have found correlations between blood 11-OH-THC and maximum speed, though existing literature does show the use of blood 11-OH-THC for correlations to cognitive assessments associated with driving.

In this analysis, we observed three novel correlations between blood CBD and driving measures. Significant correlations were found between blood CBD levels and mean speed during the dual-task driving condition at all times post-cannabis consumption, suggesting lower speed was associated with higher CBD levels. Additionally, significant correlations were found between CBD and SDSP during the dual-task driving condition at 120 minutes, and CBD and maximum speed during the dual-task driving condition at 240 minutes and 360 minutes, indicating CBD's correlation with measures of speed.

The relationship between blood CBD levels and driving measure changes are unclear, as no previous literature describe similar findings to what we saw in this analysis.

Past studies have investigated the acute effects of CBD on simulated driving, finding no significant effect[130-132]. For example, in McCartney et al., participants showed no significant change in SDLP or measures of speed at 45 and 180 minutes after the consumption of 15, 300 or 1500mg of oral CBD when compared to placebo[131]. Arkell et al. also recorded similar finding, where no significant changes were observed in SDLP at all time point when comparing placebo to 13.5mg of CBD-dominant vapourized cannabis[132]. While CBD on its own does not typically impact driving performance, the current findings suggest that CBD is associated with decreased measures of speed lasting several hours post consumption, which is novel. A potential explanation for the longevity of the effects of CBD on driving may be related to the persistence of CBD and CBD metabolites in plasma. However, a conflicting interpretation from McCartney et al. noted that low levels of residual CBD are unlikely to influence driving performance[131]. It may be important to consider that participants consumed edible cannabis containing both THC and CBD, hence the blood CBD levels may not be the only factor resulting in the current correlations. Another factor to consider is that the current correlations between blood CBD and measures of speed were seen solely during the dual task driving condition and not in the single task driving condition. This suggests that the impairing effects of CBD may be involved when there is increased complexity and increased cognitive load, such as during the dual task driving condition. Ultimately, further research into the acute effects of CBD on driving is needed.

The role of CBD in driving remains an area of ongoing research, with a growing body of studies focusing on CBD and driving-related cognition. Historically, CBD has been characterized as a non-psychoactive component of cannabis[133-135]. However, emerging

research suggests that high doses of CBD may mitigate the cognitive impairment effects of THC[136] and potentially enhance cognitive functions such as memory and may be beneficial in enhancing cognitive function, such as memory[75-77] and executive function[78], both of which are crucial for driving[74]. For instance, Solowij et al. found that chronic daily use of 200mg of oral CBD in conjunction with smoked cannabis was linked to reversal of the decrements in performance seen after THC in the Rey Auditory Verbal Learning Test (RAVLT41) and the Attention Switching Task (AST)[137]. There are conflicting results around the ameliorating effects of CBD, as multiple studies have found no significant effects of CBD lessening the effects of THC on attention[79], memory[80,81,138,139] and executive function[81,138]. For example, a study by Woelfl et al. found no significant differences in episodic and working memory tasks when comparing THC-dominant (20mg) and THC-CBD combined (800mg of CBD then 20mg of THC) consumption to a placebo[139]. In conclusion, while the current body of research on CBD and driving-related cognition is inconclusive, it underscores the need for further exploration of the complex relationship between CBD, cognition, and driving.

As the body of research around the correlation between blood THC and driving measures continues to grow, this analysis aligns with existing literature on the correlations, which suggests poor linear relationships between blood THC levels and driving impairment[15,19,22,23,27,29-33]. A recent meta-regression analysis by McCartney et al. had described that blood THC concentrations may be a poor biomarker of cannabis-induced impairment due to a weak relationship between blood THC concentrations and the impairment of cognitive skills associated with driving[68]. This is significant, as many

jurisdictions, including Canada, use *per-se* blood THC levels as a measure for impairment.

This is concerning, as the use of *per-se* blood levels may result in false-positives for recent

cannabis use[4], as blood levels of THC and its metabolites may persist in plasma, even well

outside the window associated with cannabis impairment[68]. In conclusion, this highlights

the need to continue to study the relationship between biological measures and driving

impairment and to explore other venues in detecting impairment.

Emerging research have suggested the use of alternative biomarkers for tracking

impairment, as they may be an effective way in detecting cannabis impairment. These can

include neuroimaging techniques to understand how cannabis use affects brain function

and connectivity. A recent study by Gilman et al. presents the use of functional near-

infrared spectroscopy (fNIRS) to map out oxygenated hemoglobin concentration (HbO) in

the prefrontal cortex[140]. An increase in HbO in the prefrontal cortex has previously been

associated with cannabis use, regardless of THC dose. They had found that when

combined with machine learning models, fNIRS can be used to determine impairment

from THC intoxication at an accuracy rate of 76.4%[140]. The use of such emerging

technologies can help identify cannabis impairment through alternative markers, moving

beyond the use of blood THC concentrations, which has been described as a poor

biomarker for cannabis impairment.

4.3   Testing the effectiveness of the 2ng/mL and median cut-off in detecting changes in driving measures

The comparison of the driving measures between placebo and cannabis conditions, for the above or below 2ng/mL THC cut-off, revealed a significant difference in the Below threshold group for Mean speed during both driving conditions at 120 minutes post-consumption. However, no significant difference was observed in the Above threshold group.

The use of the 2ng/mL cut-off was to demonstrate the usefulness of one of the current *per-se* blood THC limits set in Canada. The findings of this analysis are intriguing, especially when compared to a previous study by Di Ciano et al., which found a significant increase in the Standard Deviation of Lateral Position (SDLP) between placebo and drug conditions in the Above threshold group, but not in the Below threshold group[31]. That study suggested that a 5 ng/mL blood THC threshold was effective in identifying impairment in frequent cannabis smokers [31]. Contradictory results were found by Arkell et al., who investigated the usefulness of the per se limits of 1.4 and 7 ng/mL blood THC levels in impairment detection[29]. They found that approximately 50% of participants who consumed THC-dominant cannabis with blood THC levels above 7 ng/mL showed no significant driving impairment in SDLP measures 30 minutes post-consumption[29]. This raises concerns about the use of a blood THC threshold as a biomarker for impairment, as blood THC levels are not able to accurately discern between cannabis impairment and non-impairment[29]. The current analysis found contradictory results to the findings in Di Ciano et

al.[31], as the opposite findings were observed, where the Below threshold group was seen to have a significant decrease in mean speed when comparing placebo and cannabis conditions, and no significant changes were observed in the Above threshold group.

Similar to the 2ng/mL cut-off analysis, the comparison of the driving measures above or below the median blood THC level of 2.3 ng/mL revealed a significant decrease in mean speed in the cannabis condition in the Below median group at 120 minutes post-consumption. This outcome aligns with the findings from the 2 ng/mL threshold analysis, where a significant decrease in mean speed was found in below median group when comparing the cannabis condition to the no cannabis condition. Several studies have done similar analyses comparing above and below median blood THC levels. For instance, Brands et al. had found that mean speed for single task conditions showed significant difference between baseline and 30 minutes post-consumption in the High THC group, but not the low THC group[23]. This is opposite to the results of the current analysis showing significant differences in the below median blood THC group, and not the above median group[23]. Another study by Hartman et al. had produced a table that separated SDLP based on above and below median blood THC levels of 8.6 µg/L. While they did not complete a comparison analysis of the two groups, they had found a 12 % increase (in comparison to the placebo condition) in SDLP in participants with blood THC levels under the median of 8.6 µg/L and a 3% increase in SDLP in participants with blood THC levels above the median, which are similar to the our findings in this analysis but for a different driving measure[34]. Hartman et al. had explained in their results that the statistical analysis was not meaningful as certain participants achieved similar blood THC levels when consuming

both the low-THC (2.9%) and high-THC (6.7%) doses[34], resulting in repeating data points within a group. The authors had explained that the repeated data points were mostly likely due to self-titration of the inhaled dose and interindividual variability in smoking[34].

To better understand the non-significant results seen in the driving measures, an effect size was calculated to verify if any large differences would be observed between the placebo and cannabis conditions. As seen in Tables 11-15 (for the 2ng/mL analysis) and Tables 21-25 (for the median analysis), we were able to see that multiple driving measures at various timepoints for both single and dual driving conditions had revealed 'medium' to 'large' effect sizes, which indicated 'practical' differences between the placebo and cannabis conditions[141]. As the p-values generated from the Wilcoxon signed-rank test had shown that the differences between the placebo and cannabis conditions were not statistically significant, while achieving a 'medium' to 'large' effect size, this represents a lack of power for the current analysis.

A secondary effect size calculation was completed to test for any large differences between the Above and Below 2ng/mL threshold groups, or the above and below median groups of the mean differences (Placebo-Cannabis). As seen in Tables 16-20 (for the 2ng/mL analysis) and Tables 26-30 (for the median analysis), multiple driving measures revealed 'medium' and 'large' effect sizes in both analyses. No significant differences were observed in the Mann-Whitney U-test of the 2ng/mL group comparison (p>0.05). For the median group comparison, mean and maximum speed revealed a 'medium' and 'large' effect sizes, respectively, and were statistically significant (p < 0.05). This is intriguing, as that indicates that mean and maximum speed may be sensitive measures for

differentiating drivers with blood THC levels above and below 2.3 ng/mL, though the Mann-Whitney U-test can only describe that there is a difference between the two groups without specific directionality. Despite these two speed measures, all other driving measures observed no significant differences between the above and below groups, thus the current study is under-powered for the current analysis.

4.4   Limitations

The overall study is not without limitations. A principal limitation is the power related issue. While the current effect size calculations reveal 'medium' to 'large' effect sizes for several driving measures, few significant differences were observed. Thus, further research is needed with larger sample sizes.

Currently, only two blood samples were collected during each test session—one at baseline and another 120 minutes post-consumption. This limited sampling may be insufficient, as it could miss how changes in blood cannabinoid levels over time influence driving. This concern is particularly relevant when comparing smoked cannabis to edibles, as the pharmacokinetic differences between them might contribute to their varied effects on driving. Future studies should consider collecting blood at multiple time points to gain a clearer understanding of the time-dependent effects of cannabis.

It is important to note that detectable levels of THC and metabolites were observed in the blood at baseline, indicating residual cannabinoids from prior cannabis use. This raises a potential concern, as residual cannabinoids may influence driving behavior. However, it should be noted that the levels of metabolites did not vary from baseline to the

later time point in the control session. This lack of evidence of elimination over the course of the day suggests that the cannabis use was not recent. In any event, a study by Brands et al. found little evidence of residual effects from smoked cannabis on driving performance up to 48 hours after use[23]. Since the pharmacokinetics of edible cannabis differ from smoked cannabis, it remains unclear whether residual cannabinoids from edibles can similarly affect driving behavior, thus affecting the interpretation of the findings. Future research should investigate the impact of residual cannabinoids from edible cannabis on driving to better understand these potential effects.

Driving simulators, while providing a safe alternative to real-world driving and being sensitive to THC-induced effects on driving performance[16], do have limitations, as the external validity of the findings from the driving simulation scenarios should be considered. Participants are often aware they are in a simulator and may behave differently than they would in real-world driving. There may be a concern of introducing bias into the participants' driving behaviours, as current simulators cannot fully replicate the sensory experience of actual driving. Participants are also not exposed to the genuine hazards of unsafe driving, and do not face the real risks associated with unsafe driving behavior. This knowledge that they are not at actual risk of accidents may influence their driving behavior within the simulation. Nonetheless, simulator technology presents several advantages, including safety, uniformity, and objective data gathering[21,22]. Future development of driving simulation to better replicate factors of real-world driving may aid in participant immersion and would better link simulation to real-world implications.

The study's use of a rural, two-lane highway simulation may also affect the generalizability to urban driving contexts. However, findings from a rural setting can still provide insights relevant to all roadway environments. The rural environment enabled consistent data collection on driving parameters such as Standard Deviation of Lateral Position (SDLP) and speed. Additionally, rural driving was chosen to minimize the incidence of simulator sickness, which is often caused by the turning and braking associated with city driving on simulated driving, due to visual-vestibular cue mismatches[23]. It is challenging to pinpoint the impact that the basic driving scenarios had on the absence of significant changes in driving behavior within this analysis.

4.5   Future directions

While the current study sheds light on the impact of edible cannabis on driving performance, several limitations and findings underscore the necessity for further investigation. Future research endeavors should address these gaps to deepen our comprehension and establish more dependable markers for cannabis-induced impairment.

Most existing studies, including the current one, focus on the acute effects of cannabis. However, the long-term effects of chronic cannabis use on driving remain poorly understood. Future studies on the longitudinal aspects of cannabis use could provide valuable insights on the effects of chronic cannabis use, and how cannabis can affect participants on driving performance over time. As described by Colizzi et al., the current literature around tolerance and the underlying mechanism around the development of

tolerance is still poorly known[142], hence studying participants over longer periods of time may provide insight towards this. The use of longitudinal studies may allow for us to examine changes in driving behavior and cognitive function over time to identify any lasting effects of chronic cannabis use.

The exploration of alternative markers for Impairment is also a potential future direction for the current study. Blood THC levels are currently used as a marker for impairment, but the findings of this study and others suggest that this measure may not be reliable. Future research should explore alternative markers, such as neuroimaging techniques like the functional near-infrared spectroscopy mentioned previously in detecting changes in brain function and connectivity associated with cannabis use[140], as well as development of other technologies that could be more in tuned in detecting changes in driving performance and impairment. For example, A recent study investigating the use of other cannabinoid presence in exhaled breath and kinetic changes to detect recent cannabis use within the impairment window and had found that the presence of CBC and Δ9-THCV, which are lesser known cannabinoids, are only detected during the peak impairment window for smoked cannabis, which make them good candidates for future testing[143]. The development of alternative measures of impairment may provide a better link between cannabis use and driving impairment, which is currently lacking.

5   Conclusions

Overall, this thesis aimed to analyze the relationship between blood cannabinoids levels and driving measures after consuming cannabis edibles. The results of this thesis reinforce the current notion that blood THC alone is an inadequate marker for impairment detection, as no correlations were observed between blood THC and any of the driving measures. On the contrary, the findings support the idea that THC metabolites, like 11-OH-THC, may be better proxies for representing the effects of THC and in assessing correlations. With a growing body of research around the effects of CBD on driving-related cognition, the negative correlations between blood CBD and measures of speed seen in this thesis adds to this body of research, possibly igniting future research around the role of CBD on driving. The examination of 2 ng/mL and median blood THC levels for impairment detection challenges the current use of blood THC levels in *per-se* legislation, as most driving measures showed no significant difference between placebo and cannabis conditions for participants above and below the threshold. Future research is essential to further explore the observations of this thesis and would be beneficial in the development for more reliable measures of cannabis impairment, which can help develop new policies and improve road safety.

6   References

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