CANNABIS USE AND CARDIOMETABOLIC RISK FACTORS

CANNABIS USE AND CARDIOMETABOLIC RISK FACTORS IN PATIENTS WITH PSYCHIATRIC CONDITIONS

By LISA OWUSU SARPONG, H.B.Sc.

A Thesis Submitted to the School of Graduate Studies in Partial Fulfilment of the Requirements for the Degree Master of Science

McMaster University MASTER OF SCIENCE (2020) Hamilton, Ontario (Medical Sciences)

TITLE: Cannabis Use and Cardiometabolic Risk Factors in Patients with Psychiatric Conditions

AUTHOR: Lisa Owusu Sarpong, H.B.Sc. (University of Toronto)

SUPERVISOR: Dr. M. Constantine Samaan

NUMBER OF PAGES: ix, 42

LAY ABSTRACT

The endocannabinoid system regulates several processes in the body via endocannabinoid signaling, and cannabinoids found in cannabis can change endocannabinoid system function. Cardiovascular events and changes in appetite have been noted with cannabis use, and this is especially important in some vulnerable populations at risk of increased cannabis use; one of these groups include patients with psychiatric conditions who tend to use cannabis but also already have an increased cardiometabolic risk. In this thesis, the relationship between cannabis use and cardiometabolic risk was examined in 200 patients, and patterns and determinants of cannabis use explored.

Our results demonstrated that of the 79 cannabis users, most consumed cannabis daily, and had a moderate cannabis use disorder. On average, users began cannabis consumption at 15 years of age and for an average duration of 14 years. Moderate cannabis use was not related to cardiometabolic risk in these patients.

Our data demonstrate the need to prevent or slow the progression of cannabis use disorder in these patients and the importance of reducing early exposure of adolescents to cannabis.

ABSTRACT

Introduction: The homeostatic role of the endocannabinoid system (ECS) is mediated through the actions of endocannabinoids. Intake of exogenous cannabinoids found in *Cannabis sativa* alter the function of the ECS which may then impact other organ systems. Use of cannabis has been inconsistently linked to adverse cardiometabolic outcomes. Rates of cannabis use are high among patients with psychiatric conditions who are already at higher risk of cardiometabolic diseases when compared to the general population. Cannabis use patterns and cardiometabolic risk variables in this population need further study to clarify the links between use and outcomes.

Methods: Patients with psychiatric conditions from the St. Joseph's Healthcare Hamilton Hospital were enrolled into the Cannabis and Physical Health study. Sociodemographic data, medical history, cigarette use, and cannabis use patterns were collected. In addition, cardiometabolic profile data were collected including body mass index, blood pressure, lipids, and HbA1c. Multivariable regression analyses were conducted, and a Bonferroni correction applied.

Results: This cross-sectional study enrolled 200 patients (female: n=86, 43.0%), 18 years of age and older. Among 79 cannabis users (female: n=34, 43.0%), the majority (n=53, 67.1%) consumed cannabis daily and had a diagnosis of a moderate cannabis use disorder (CUD; n=57, 72.2%, CUD score = 4.3 ± 3.4). Use of cannabis was initiated on average at 15.2 ± 3.5 years of age and used for an average of 13.5 ± 11.0 years. There was no association between cannabis use and cardiometabolic risk factors when adjusted for age,

sex, psychiatric diagnosis, antipsychotic medication use, and cigarette smoking (P>0.006 for all outcomes).

Conclusions: Our findings indicate that in this sample of patients with psychiatric diagnoses, patients who use cannabis had a similar cardiometabolic profile to non-users. Patterns of cannabis use highlight the importance of reducing cannabis consumption and preventing or slowing the progression of CUD in this population, as well as limiting adolescent exposure to cannabis.

TABLE OF CONTENTS

LIST OF FIGURES AND TABLES

LIST OF ALL ABBREVIATIONS AND SYMBOLS

2-AG 2-arachidonoylglycerol

AEA Arachidonoylethanolamide

BMI Body mass index

cAMP Cyclic adenosine monophosphate

CB_1 Cannabinoid type 1

CB_2 Cannabinoid type 2

CBD Cannabidiol

CUD Cannabis use disorder

ECS Endocannabinoid system

FAAH Fatty acid amide hydrolase

GLP-1 Glucagon-like peptide 1

HbA1c Hemoglobin A1c

HDL High-density lipoprotein

LDL Low-density lipoprotein

MAGL Monoacylglycerol lipase

NPY Neuropeptide Y

T2DM Type 2 diabetes mellitus

THC Tetrahydrocannabinol

THCV Tetrahydrocannabivarin

WT Wild type

PREFACE

I would like to thank Dr. Samaan for supervising me and encouraging me to read, grow and learn. I would also like to thank Dr. De Souza for his kindness and always being available to answer my statistical questions on short notice. I am grateful to Dr. Z. Samaan for her guidance and help in overcoming recruitment and data acquisition challenges. Dr. Thabane was also instrumental in ensuring I was on the right track with my statistical analyses. For this, I am most grateful.

I would also like to thank Kuan-Wen Wang, a previous master's student with the Samaan Research Group, for her invaluable advice during my master's program. Jacqueline Hudson was very helpful from an administrative perspective. Finally, I would like to express my gratitude to the nurses and clinical staff that helped with obtaining medical information for the study, the patients that participated in this study and Jesus for being with me throughout this journey.

I acknowledge that I recruited the patients, performed the statistical analysis, and interpreted the results with help from my supervisor and supervisory committee team. I also wrote the thesis and the paper, which was reviewed by all co-authors prior to submission.

CHAPTER 1: INTRODUCTION

The endocannabinoid system

Interest in the psychoactive actions of cannabis led to the characterization of the endocannabinoid system (ECS) in the late 1990s (1-3). Thirty years prior to this discovery, Δ^9-tetrahydrocannabinol (THC) was isolated, which was established as the main psychoactive compound of cannabis (4). As the search for endocannabinoid receptors was proceeding, several groups identified and cloned the cannabinoid type 1 (CB_1) (5, 6) and cannabinoid type 2 (CB_2) receptors (7). THC binds to both receptors. Subsequently, the endogenous ligands (endocannabinoids) that bind the CB_1 receptors were discovered (8-10).

CB_1 and CB_2 receptors are $G_{i/o}$-protein-coupled receptors that are found in the central and peripheral nervous system and other organs and cells (11). CB_1 receptors are largely present in the cortex, hippocampus, amygdala, basal ganglia, hypothalamus, and cerebellum (11); CB_2 receptors are present primarily in microglia (7, 12) and hematopoietic cells (13). Apart from being localized in the brain and immune cells, endocannabinoids and their receptors are also present in metabolic organs, including the adipose tissue, liver, pancreatic islets, and skeletal muscle (14-17).

Endocannabinoids and the machinery involved in their synthesis and degradation also form part of the ECS. Although there are various types of endocannabinoids within the human body, 2-arachidonoylglycerol (2-AG) is the most abundant, and arachidonoylethanolamide (AEA) is less ubiquitous, but also well-described (1, 18). The

effects of these bioactive lipids are mediated by CB_1 and CB_2 receptors to which they bind with varying efficacy (18).

Modulatory role of Endocannabinoids in the nervous system

In the central nervous system, the components of the ECS are placed at synapses to effectively modulate neurotransmission in a retrograde fashion (19). Endocannabinoid precursors are housed within lipid membranes of post-synaptic axon terminals. Binding of a neurotransmitter at the post-synaptic terminal activates the production of endocannabinoids (19). The endocannabinoids are subsequently released into the synaptic cleft, bind to the transmembrane cannabinoid receptors on the pre-synaptic lipid membrane and inhibit the release of inhibitory or excitatory neurotransmitters from the pre-synaptic axon terminal (19). After their release, the 2-AG and AEA are efficiently degraded by their distinctive catabolic enzymes (monoacylglycerol lipase (MAGL) and fatty acid amide hydrolase (FAAH), respectively (20)).

This arrangement allows the ECS to carry out its pre- and postnatal functions, including axon guidance and growth (21), the modulation of neuronal proliferation and migration in the fetus (1, 22), and regulation of adult neurogenesis (1, 23). This neuromodulatory system is thus tightly regulated to maintain homeostasis (18).

Neuropsychological effects of THC

The well-known neuropsychological effects associated with cannabis use have been attributed to THC and its interaction with CB_1 receptors (24). Short-term effects of cannabis use include impaired working memory, motor coordination and judgement,

amotivation and the manifestation of paranoia and psychosis with higher doses (25). Cannabis use has also been shown to have long-term effects, including risk of addiction, impaired cognition, lower educational and occupational attainment, and reduced life achievement (25). Altered development of the prefrontal cortex, hippocampus and subcortical networks can also ensue from cannabis use, as THC disrupts the formation of connections between axons resulting in fewer neural connections in these regions of the brain (26). Long-term effects occur more frequently with earlier onset of cannabis use as the brain continues to develop during adolescence and into early adulthood which is a vulnerable period (27).

Metabolic function of Endocannabinoids in peripheral tissues

As noted above, the endocannabinoids function as retrograde neurotransmitters in the central nervous system, but also participate in autocrine, paracrine and intracellular signaling in peripheral tissues to regulate the many physiological processes with which the ECS is involved (14, 28). Early research focused on studying the effects of the ECS in relation to the central nervous system, due to the abundance of CB_1 receptors in the brain and the ability of exogenous cannabinoids to bind to them (28).

However, endocannabinoids are present outside neural tissue, and may act as intermediates for other biologically active molecules, including arachidonic acid in the synthesis of prostaglandins (29). Its involvement in diverse biological activities suggests that dysregulation of endocannabinoid levels may negatively alter other pathways and implicates them in pathophysiological processes (30).

The ECS has also been recognized for its essential role in energy homeostasis, stimulating appetite and caloric intake, and regulating lipid and glucose metabolism (15-17).

Stimulation of appetite and caloric intake

The ECS has been recognized for its crucial neuroendocrine role in inducing feeding in response to transient food deprivation through hypothalamic actions (31, 32). In mice, low dose arachidonoylethanolamide (AEA), an endogenous cannabinoid, that was administered directly to the hypothalamus, resulted in an increase in food intake (33, 34). Furthermore, mice treated with the CB_1 receptor antagonist, AM251, had a dose-dependent reduction in food intake (35).

Evidence from CB_1 knockout mice supports these findings and demonstrates that endocannabinoid action on CB_1 receptors is essential for appetite stimulation. Caloric intake was significantly lower in fasted CB_1 knockout mice compared to fasted wild-type (WT) mice (36). Administering a CB_1 antagonist to both strains reduced food intake of WT mice to levels observed in knockout mice, while the feeding behaviour of CB_1 knockout mice was unaffected as predicted (36). In another study, administration of the potent orexigenic (food-intake stimulating) neuropeptide Y (NPY) induced overeating in fed WT mice, whereas NPY had no effect on CB_1 knockout mice (37). Subsequent administration of a CB_1 receptor antagonist nullified the effect of NPY in WT mice (37), indicating that the presence of orexigenic neuropeptides is not sufficient to compensate for a lack of endocannabinoid action.

Further, genetically obese leptin and leptin receptor deficient (*ob*/*ob and db*/*db*) mice provide evidence that appetite stimulation due to high levels of hypothalamic endocannabinoids may lead to obesity (36). Blocking CB_1 receptors through use of the antagonist, Rimonabant, decreased food intake acutely in *ob*/*ob* and *db*/*db* mice compared to controls (36). When Rimonabant was administered over a seven-day period, *db*/*db* mice experienced a reduction in body weight compared to controls, suggesting that endocannabinoids are important contributors to overeating and the development of obesity (36).

Lipid metabolism

The ECS regulates lipid metabolism through mechanisms independent of centrally induced food intake effects. Mouse epididymal fat pads were found to express CB_1 receptors (32). Removal and treatment of cultured adipocytes with a CB_1 agonist increased the activity of lipoprotein lipase, an enzyme whose action permits free fatty acid uptake and storage in adipocytes, while pre-treatment of cells with a CB_1 receptor antagonist led to attenuation of lipoprotein lipase activity (32).

In hepatocytes, lipogenesis is stimulated by CB_1 receptor activation (38). The rate of *de novo* fatty acid synthesis was doubled in WT mice pretreated with a CB_1 receptor agonist, but no increase was observed in mice administered the CB_1 antagonist, Rimonabant, or in CB_1 knockout mice (39).

Increased fatty acid synthesis and intake of dietary fat contribute to the deposition of fat in hepatocytes (40). Accordingly, Osei-Hyiaman and colleagues (2005) observed

the occurrence of fatty liver, in conjunction with higher levels of hepatic AEA and upregulation of CB_1 receptor expression solely in WT mice fed a high-fat diet (39). These findings confirmed the role of the ECS in the development of diet-induced hepatic steatosis and obesity in mice (38, 39).

Glucose metabolism

The attempts to define the location of CB_1 receptor expression and endocannabinoid synthesis in the pancreas yielded conflicting results (41-43). However, González-Mariscal et al. (2016) recently elucidated the location, role and mechanism of pancreatic CB_1 receptors and endocannabinoids in a series of experiments demonstrating that stimulation of CB_1 receptors in pancreatic β-cells inhibits insulin secretion and promotes insulin resistance in mice and humans (44, 45). When a rise in glucose stimulates release of glucagon-like peptide 1 (GLP-1) from enteroendocrine cells, GLP-1 exerts its effect on G_s-coupled protein receptors located on the insulin-secreting β-cells of the pancreatic islets (44). Binding of GLP-1 to its receptor leads to an increase in the enzymatic activity of adenylyl cyclase and a rise in cyclic adenosine monophosphate (cAMP). Elevated cAMP enhances β-cell insulin secretion (44, 46).

An increase in glucose levels also stimulates the production of endocannabinoids (42, 43). In one experiment, the addition of AEA or 2-AG, the endogenous cannabinoids, and their binding to $G_{i/o}$-coupled CB_1 receptors in a mouse insulinoma cell line led to the attenuation of previously elevated levels of cAMP and insulin secretion by 40% (44). A subsequent experiment was conducted in a cell culture of human islet cells to confirm the

inhibitory effects of CB_1 receptor activation on insulin secretion. The attenuation was even more pronounced in human islet cells with a 65% reduction in cAMP levels and 50% reduction in insulin secretion (44).

Finally, glucose uptake is directly altered by the ECS. Rimonabant-mediated antagonism of CB_1 receptors on cultured L6 myoblasts led to an increase in glucose uptake (47). Similarly, treatment with a CB_1 receptor antagonist increased the rate of glucose uptake in the soleus muscle of genetically obese leptin deficient (*ob/ob*) mice (48), and incubation of human skeletal muscle cells with AEA reduced phosphorylation of Akt, a protein largely responsible for inducing glucose uptake in response to insulin (49, 50). When preincubated with AM251, a CB_1 receptor antagonist, the AEA-induced inhibition of Akt phosphorylation was prevented (49).

In summary, the effects of the endocannabinoid system in the regulation of metabolism are important. In the hypothalamus, endocannabinoids stimulate appetite and enhance caloric intake. They also contribute to the storage of fat in adipocytes and hepatocytes. In the pancreatic islets, endocannabinoids decrease insulin secretion, while in muscle, endocannabinoid exposure is linked with reduced insulin action.

Exogenous cannabinoids

Much work has been done to characterize the ECS in order to better understand the effects of exogenous cannabinoids on normal ECS functioning and health. Exogenous cannabinoids, including the phytocannabinoids found in the plant, *Cannabis sativa*, have the ability to bind to CB_1 and CB_2 receptors (14). Of note, Δ^9-tetrahydrocannabinol (THC)

is the major psychoactive compound of cannabis and an agonist of both CB_1 and CB_2 receptors (30). However, THC is not selective as are endocannabinoids (14) and may therefore bind to the CB_1 and CB_2 receptors in the body, which has made the widespread use of cannabis particularly concerning.

Cardiometabolic effects of THC

The cardiometabolic effects of cannabis use are less well-known, despite the fact that there is some evidence to implicate THC in adverse cardiometabolic outcomes (51). The cardiometabolic actions of THC have been studied through cannabis and synthetic THC, including Dronabinol (14).

The seminal study conducted by Greenberg and co-workers (1976) was the first to examine variations in feeding behaviour and body weight in participants using a specified amount of THC (2.06% THC in 1 g cannabis cigarette). Initially, an increase in both caloric intake and weight was observed in the cannabis-using participants compared to non-users. After the fifth day, caloric intake was stable, yet weight continued to increase till the end of the 21-day drug-taking phase (51). In later placebo-controlled cross-over trials, Dronabinol, provided to patients with Alzheimer's disease (2.5 mg THC) over a six-week period (52) or severe anorexia nervosa (5 mg THC) (53) over a four-week period, also resulted in a significant increase in weight. These studies suggest that acute, low doses of THC stimulate appetite, food consumption and modest weight gain in healthy individuals and patients with neurocognitive and psychiatric disorders.

With changes in diet, fluctuations in cardiometabolic effects can be quickly detected. In fact, a three-week study involving normal-weight participants demonstrated elevation of cholesterol, triglycerides and plasma glucose that began within one week of commencing a high-calorie diet (54).

Further, the risk of metabolic dysfunction and cardiovascular conditions increases with excess fat mass (55). It has been long established through large epidemiological and prospective studies that the risk of type 2 diabetes increases with increased BMI and measures of central adiposity including waist circumference, and waist-to-hip ratio increases (56-58). In terms of cardiovascular disease, Larsson et al. examined the association between cardiovascular disease and genetic variants predicting increased BMI and fat mass in a large study of 367,703 participants. Using Mendelian randomization, they determined that genetic predisposition to increased BMI and fat mass is in fact associated with an increased risk of cardiovascular conditions including ischaemic stroke, hypertension and heart failure (55). However, lifestyle choices, including regular physical activity and a healthy diet can decrease these risks (55).

Cannabis use and association with cardiometabolic health

In the last 40 years, there has been a surge in the selective breeding to increase the concentration of THC with agricultural practices of cannabis cultivation (59). Present-day strains average as high as 15% in THC content, a five-fold increase from the 1980s (60). Not only is cannabis potency rising, but also cannabis use is on the rise, with 188 million users worldwide as of 2019 (59). Use is likely to continue to increase as perceptions

continue to change in favour of use, cannabis gains increasing social acceptance and the world continues to move towards its decriminalization and legalization (61). Given the ubiquity of cannabis use, the cardiometabolic effects of cannabis use have been comparatively underexamined and necessitate additional study.

The neuropsychiatric and potential adverse cardiometabolic effects observed with use of THC may be amplified with recent increases in THC content and cannabis use. Further, among vulnerable populations, including patients with psychiatric disorders, the effects of cannabis use may additionally exacerbate their already present risk of cardiometabolic disorders, due to a higher prevalence of cannabis use in this population compared to the general population (62).

Examination of the association of cannabis use with cardiometabolic health has produced conflicting results with case reports detailing cardiovascular events (63-65) and studies demonstrating better or at least not worse cardiometabolic profiles in cannabis users when compared to non-users (66-68). Furthermore, results from cannabis use in past studies involving patients with psychiatric disorders have limited generalizability as cannabis amounts and frequencies of use were inadequately measured (69, 70).

Aims

In light of the conflicting evidence base linking cannabis use with cardiometabolic health, we conducted a cross-sectional study with the following aims:

1. To examine whether cannabis use status in patients with psychiatric conditions is associated with cardiometabolic risk factors including body mass index (BMI),

blood pressure, lipids (total cholesterol, high-density lipoprotein (HDL)-cholesterol, low-density lipoprotein (LDL)-cholesterol, triglycerides), and glycemia (hemoglobin A1c (HbA1c)).

2. To explore cannabis use patterns in patients with psychiatric conditions.

CHAPTER 2: THE ASSOCIATION BETWEEN CANNABIS USE AND CARDIOMETABOLIC RISK FACTORS

The association between cannabis use and cardiometabolic risk factors in patients with psychiatric conditions

Authors
Lisa Sarpong[1,2]
Zainab Samaan[3,4]
Lehana Thabane[4,5,6,7]
Russell J de Souza[4]
M. Constantine Samaan[1,2,4,8]

Lisa Sarpong: sarponlo@mcmaster.ca
Zainab Samaan: samaanz@mcmaster.ca
Lehana Thabane: thabanl@mcmaster.ca
Russell J de Souza: desouzrj@mcmaster.ca
M. Constantine Samaan: samaanc@mcmaster.ca

Institutional affiliation:
[1] Department of Pediatrics, McMaster University, Hamilton, Ontario, Canada
[2] Division of Pediatric Endocrinology, McMaster Children's Hospital, Hamilton, Ontario, Canada
[3]Department of Psychiatry and Behavioral Neurosciences, McMaster University, Hamilton, Ontario, Canada
[4]Department of Health Research Methods, Evidence and Impact, McMaster University, Hamilton, Ontario, Canada
[5]Department of Anesthesia, McMaster University, Hamilton, Ontario, Canada
[6]Centre for Evaluation of Medicines, St. Joseph's Healthcare Hamilton, Ontario, Canada
[7]Biostatistics Unit, St. Joseph's Healthcare, Hamilton, Ontario, Canada
[8]Michael G. DeGroote School of Medicine, McMaster University, Hamilton, Ontario, Canada

Short title: Cardiometabolic health and cannabis use in psychiatric patients

Keywords: cannabis; psychiatric disorders; cardiometabolic risk; HbA1c, BMI; lipid profile

Corresponding Author's Contact Information:

Dr. M. Constantine Samaan
Department of Pediatrics, McMaster University, Hamilton, Ontario, Canada
1200 Main Street West, HSC-3A57
Hamilton, Ontario L8N 3Z5
E-mail: samaanc@mcmaster.ca

Name and address of person to whom reprint requests should be addressed:
Dr. M. Constantine Samaan
Department of Pediatrics, McMaster University, Hamilton, Ontario, Canada
1200 Main Street West, HSC-3A57
Hamilton, Ontario L8N 3Z5

Grants or fellowships supporting the writing of the paper:
There are no grants or fellowships supporting the writing of this paper

Disclosure summary: The authors have no conflicts of interest to disclose.

Abstract

Context: Cannabis use has been inconsistently linked to adverse cardiometabolic effects. Patients with psychiatric disorders have increased cardiometabolic risk and use cannabis more than the general population, yet use patterns are unknown.

Objective: This study examined the association between cannabis use and cardiometabolic risk factors in patients with psychiatric disorders and explored use patterns post-legalization.

Design and Setting: The Cannabis and Physical Health study is a cross-sectional cohort study conducted at St. Joseph's Healthcare Hamilton Hospital in Canada over a 1.5-year period.

Patients: A total of 200 patients with psychiatric conditions who provided informed, written consent were enrolled.

Main outcome measures: Cardiometabolic risk factors measured include body mass index, blood pressure, total cholesterol, high-density lipoprotein, low-density lipoprotein, triglycerides and HbA1c.

Results: Study participants consisted of 121 non-users (female: n=52, 42.9%) and 79 users (female: n=34, 43.0%) of cannabis. Users tended to consume cannabis daily (n=53, 67.1%) and most had a moderate cannabis use disorder (n=57, 72.2%). On average, onset of cannabis use began at 15.2 ± 3.5 years old and cannabis was used for an average of 13.5 ± 11.0 years. Users preferred consuming joints (n=59, 74.7%) and *Cannabis indica* strains (n=27, 34.2%). There was no association between cannabis use status and

cardiometabolic risk factors when adjusted for age, sex, psychiatric diagnoses, use of antipsychotic medications and cigarette smoking (P>0.006 for all outcomes).

Conclusions: Our results suggest that cannabis use does not affect cardiometabolic risk in patients with psychiatric conditions. However, use patterns indicate the need to prevent or slow progression of CUD severity and decrease adolescent exposure to cannabis.

Introduction

Cannabis is the most commonly used recreational drug worldwide (1). Its use will likely increase as more countries adopt decriminalization and legalization measures, which is currently limited to Uruguay, Canada, and some USA states (2, 3).

Cannabis is generally perceived by the public as a benign, naturally occurring substance, a view that has persisted post-legalization (3). Cannabis is a complex compound containing more than 400 substances that include its primary psychoactive constituent, tetrahydrocannabinol (THC) (4, 5). THC is also known for its ability to stimulate appetite and increase caloric intake (6-9). Due to its orexigenic effects, one pilot study and several randomized controlled trials have been conducted to assess its use as a potential appetite stimulant to promote weight gain in patients with AIDS and HIV-induced anorexia (10-13).

In the general population increased caloric intake, even with minimal weight gain, results in increased levels of serum glucose, insulin, triglycerides, and total cholesterol (14). However, while this is the case under experimental conditions, the use of cannabis in the general population has produced conflicting effects on cardiometabolic health.

Cannabis use has been associated with enhanced visceral adiposity in some studies (15), yet in other studies the increase in cannabis use was associated with lower waist circumference and body mass index (BMI) (16, 17). Another longitudinal study found no association between cannabis use and BMI (6).

The evidence is also inconsistent when it comes to cannabis effects on insulin secretion and lipids. Cannabis use was associated with lower circulating insulin levels (16), while another study reported no differences in insulin, glucose, triglycerides, or cholesterol but that cannabis use is associated with reduced high-density lipoprotein (HDL) levels (15). Similarly, a study found that use of cannabis did not result in better or worse fasting plasma glucose, total cholesterol, HDL or triglyceride levels (6).

Existing literature has also associated cannabis use with cardiovascular events and arrythmias in the general population, and data have also described incidences of acute ischemic stroke and cardiovascular events in adult users (18-22). These findings suggest that the relationship between cannabis use and cardiometabolic risk factors is complex and requires further elucidation.

With recent legalization, there are concerns surrounding increased access by vulnerable populations who may be disproportionately affected by its potentially harmful effects. Patients with psychiatric conditions have increased rates of cannabis consumption (23, 24). The lifetime rate of cannabis use disorders is three times greater in patients with schizophrenia than it is in the general population (24, 25). Further, patients with psychiatric diagnoses, including schizophrenia spectrum and mood disorders, already have a higher risk of cardiometabolic outcomes due to the high prevalence of metabolic

syndrome in this population (26-29). In addition, weight gain from certain antipsychotic, mood-stabilizing and antidepressant medications does play a part in driving cardiometabolic risk (30-33). The consumption of cannabis may further compromise the physical and mental health of this population.

We hypothesized that cannabis use was associated with increased cardiometabolic risk profile in patients with psychiatric disorders. The aim of this study was to determine the associations between cannabis use and cardiometabolic risk factors among patients with psychiatric conditions. This study also explored cannabis use patterns among participants as previous studies have not fully quantified cannabis dose and patterns of use.

Materials and Methods

Study population

The Cannabis Use and Physical Health Study is a single-site cross-sectional cohort study approved by Hamilton Integrated Research Ethics Board (HIREB #4672) and conducted in conformity with the Declaration of Helsinki. Participants were recruited from the West 5th campus of St. Joseph's Healthcare Hamilton (SJHH), Hamilton, Canada between June 4th, 2018 and November 26th, 2019. Participants provided informed written consent, were 18 years of age or older and were admitted to SJHH for a psychiatric condition. Patients who had used cannabis within 30 days of the interview date were considered current users. Participants who had never used cannabis or had not used it in the past 30 days were considered non-users. These participants were combined into one group (non-

users) as there were relatively few participants who had never used cannabis (n = 29). The details of study recruitment are reported in Figure 1.

Study population characteristics

Trained research personnel approached and consented eligible patients. Sociodemographic information including age, sex, ethnicity, marital status, level of education, employment status, occupation, and income support were collected. Age of cigarette smoking initiation and number of cigarettes smoked per day were also collected.

Cannabis use

Data related to the details of cannabis use were collected from users. Information collected included age of cannabis initiation, total years of use, total duration of cannabis use, amount and frequency of cannabis use, amount spent on cannabis per week, method of consumption and type of cannabis used. The Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5) criteria were used for psychiatric diagnoses including substance use disorders (34).

To calculate cannabis amounts, participants were asked to quantify the amount of cannabis used per occasion in grams. Quantities not reported in grams were converted to grams using reliable sources from previous studies (35, 36). The weights of a surrogate substance, as determined by regular cannabis users, was used to quantify cannabis amounts in grams (35), and an addiction expert estimated cannabis amounts used (36). We considered a joint to be equivalent to 0.66 grams (35), and responses, including " a few puffs of a joint" or "less than a joint" to be 0.33 grams (36). Several patients reported

number of grams consumed per day. To standardize responses, all responses were treated as minimum amount of cannabis used per day (g).

Current psychiatric diagnoses and medications used were obtained from the patients and confirmed from the medical charts.

All physical measurements were taken by trained healthcare professionals. Height (cm) and weight (kg) were measured closest to the 0.1 cm using a digital scale (Eye Level Digital Beam Scale, Model 500KL, Health o meter Professional, Illinois, USA). BMI was calculated from the height and weight measurements as the weight divided by the square of height (kg/m^2) (37). Blood pressure readings were obtained using digital device monitor (Connex Vital Signs Monitor, WelchAllyn, New York, USA).

Laboratory tests

Total cholesterol, low-density lipoprotein (LDL) cholesterol, HDL cholesterol, triglycerides and HbA1c levels were processed at the Core Lab of SJHH (Charlton Campus) using standard clinical laboratory procedures and machines.

Statistical analyses

All data were analyzed using IBM SPSS Statistics for Windows, version 26.0. (IBM Corp., Armonk, N.Y.) (38). Sociodemographic variables, clinical characteristics, laboratory values and cannabis use patterns were reported as means (standard deviations) or frequencies (percentages) for continuous and categorical variables, respectively. Study outcomes were assessed for normal distribution using their standardized residuals. To address the primary outcome of the study, multivariable linear regression was employed,

and statistical significance set at an alpha of p-value < 0.006 to correct for multiple testing (Bonferroni correction= p-value < α/n).

Results

The sociodemographic and clinical characteristics of this study population are presented in Table 1. Participants were primarily male (n=114, 57.0%), European (n=141, 70.5%), unmarried (n=123, 61.5%), and unemployed (n=149, 74.5%). Cannabis users formed 40% of participants (n=79; male n=45, 57%) and were more likely to be younger and to be recipients of Ontario disability income support compared to non-users.

In relation to psychiatric diagnoses, bipolar disorder (n=20, 25.3%) and schizophrenia spectrum disorders (n=16, 20.2%) were the most common diagnoses among users. Conversely, non-users (n=48, 39.7%) were commonly diagnosed with depressive disorders. The majority of cannabis users (n=55, 69.6%) compared to non-users (n=50, 41%) smoked cigarettes, and users smoked more cigarettes per day than non-users (users: 9.7 ± 11.0; non-users: 5.6 ± 9.6).

Both groups were overweight (26.7 ± 6.8 kg/m^2 vs. 28.4 ± 6.7 kg/m^2), and non-users of cannabis had similar mean systolic blood pressure (121.9 ± 11.6 mmHg vs.126.8 ± 16.8 mmHg) and mean diastolic blood pressure values (78.1 ± 8.7 mmHg vs. 79.4 ± 9.2 mmHg).

Most of the physical examination data were within normal limits (Table 1). Regarding the laboratory data (Table 2), cannabis users and controls had comparable total cholesterol (4.7 ± 1.1 mmol/L vs. 4.8 ± 1.1 mmol/L), HDL (1.3 ± 0.5 mmol/L vs. 1.3 ± 0.4 mmol/L), LDL (2.7 ± 0.9 mmol/L vs. 2.8 ± 0.9 mmol/L), triglyceride (1.5 ± 0.7

mmol/L vs. 1.7 ± 0.8 mmol/L) and HbA1c (5.4 ± 0.% vs. 5.5 ± 1.1%) levels, reflecting good health.

We then performed a multivariable linear regression to establish whether cannabis use was independently associated with the cardiometabolic risk factors (Table 3). No association between cannabis use status and cardiometabolic risk factors was evident after adjustment for age, sex, psychiatric diagnosis, use of antipsychotic medications, and cigarette smoking.

To assess the patterns of cannabis use, participants were asked questions related to their cannabis consumption, and the DSM-5 criteria was used to evaluate whether participants had a cannabis use disorder (CUD) (Table 4). The majority of users (n=53, 67.1%) consumed cannabis daily and a large proportion of users (n=57, 72.2%) had a moderate CUD (CUD score = 4.3). Users initiated cannabis on average at 15.2 ± 3.5 years of age and were using it for approximately 13.5 ± 11.0 years.

Users (n=59, 74.7%) preferentially smoked cannabis as a joint and on average consumed at least 1.6 grams per day (equivalent to 2.5 joints/day) (35). Users mainly consumed *indica* (n=27, 34.2%) and *sativa* (n=20, 25.3%) cannabis strains.

Discussion

Cannabis use is climbing due to the relaxation of regulations surrounding its use. While there are public perceptions that cannabis is a natural and rather harmless product, evidence suggests that there may be adverse psychiatric and cardiometabolic effects.

This study evaluated the association of cannabis use with cardiometabolic risk factors. There was no association between cannabis use and body mass index, blood

pressure, glycemia and lipid homeostasis when potential confounders were adjusted for in the analysis.

Our findings are similar to a large 15-year study of racially diverse young adults (6), and a large cross-sectional study of the general population (16) which found no difference in BMI (6, 16), systolic and diastolic blood pressure (6, 16), total cholesterol (6), HDL (6), triglycerides (6, 16) or hemoglobin A1c (16) between users and nonusers after adjusting for alcohol use, physical activity, and diet (6, 16). Although THC has been implicated in stimulating appetite and increasing caloric intake (6-9), the absence of an increase in cardiometabolic risk factors may be due to an increased metabolic rate in users of cannabis, offsetting increased caloric intake. In a small placebo-controlled study, use of cannabis led to an increase in metabolic rate (39). Other cannabinoids present in cannabis, including tetrahydrocannabivarin (THCV), may contribute to this effect. The administration of THCV to dietary-induced obese mice augmented energy expenditure but had no effect on caloric intake or body weight (40).

Conversely, other general population-based studies demonstrated conflicting cardiometabolic impacts for cannabis use. A small study of 60 participants found worse cardiometabolic profiles in cannabis users compared to nonusers (15). An increased cardiometabolic risk (higher systolic and diastolic blood pressures, and lower HDL levels) was observed in this study but no adjustments were made in the analyses.

Another study found similar results when examining cardiometabolic risk factors in acute cannabis use (41). Although acute use of cannabis has been associated with increased blood pressure and heart rate, chronic cannabis use has been linked to tolerance

(41-43). With prolonged use, the cannabinoid 1 receptors (CB1R) decrease in density and its signalling is downregulated (42).

In contrast, lower BMI values were observed among users in large cross-sectional studies of the general U.S. population, including samples drawn from the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) (44), the National Comorbidity Survey-Replication (NCS-R) (44), and the third National Health Examination Survey (NHANES III) (8). Although BMI values were lower in cannabis users of the NESARC and NCS-R compared to non-users, the differences in BMI were only statistically significant but not likely clinically significant (44). Similar to our study, users and non-users were overweight, yet BMI values were slightly higher in the user group (NESARC: 25.6 kg/m^2 in cannabis users vs. 26.8 kg/m^2 in non-users; NCS-R: 25.6 kg/m^2 in cannabis users vs. 27.1 kg/m^2 in non-users) (8, 44). In the NHANES III, when age, sex, caloric intake, and cigarette smoking were considered, heavy users also had a lower BMI than non-users (8). However, the study did not control for physical activity or alcohol use as did others studies finding no difference (6, 16).

Our results differ from longitudinal studies conducted in psychiatric populations which found an inverse association between use of cannabis and cardiometabolic risk factors, including BMI, diastolic blood pressure and total cholesterol (45-47). Differences between these studies and our findings may exist for several reasons.

The broad inclusion of participants with differing psychiatric conditions may have contributed to discrepancies in findings. The study conducted by Bruins et al. in patients with severe mental illness largely included patients with schizophrenia spectrum disorders

(90.4% of all participants) (45). Similarly, the other two studies limited inclusion to patients with first-episode non-affective psychosis (46) or first-episode schizophrenia spectrum disorders (47). We did not limit recruitment by psychiatric diagnosis, and this approach is useful in examining which patients are more prone to cannabis use-related cardiometabolic disorders. In our study, participants were mainly diagnosed with depressive (n=58, 29.0%), bipolar (n=48, 24.0%) or schizophrenia spectrum or other psychotic disorders (n=34, 17.0%). However, bipolar (n=20, 25.3%) and schizophrenia spectrum or other psychotic disorders (n=16, 20.2%) were the most common diagnoses among users of cannabis, followed by personality (n=11, 13.9%), depressive (n=10, 12.7%) and anxiety (n=10, 12.7%) disorders.

In several studies, cannabis dose and frequency were not quantified (46, 47) or were inadequately measured (45). For example, in one study, cannabis use was measured as the number of joints per week, but the amount of cannabis in each joint was not reported (45). Cannabis intake has been shown to have dose-dependent physiological effects (48). Adequate quantification and larger sample sizes would allow for better interpretation of cannabis effects and comparison between groups.

Although no association was found between cannabis use status and cardiometabolic risk factors in adult patients with psychiatric conditions, cannabis use has been implicated in impeding treatment effectiveness, increasing risk of developing other substance use disorders and prolonging hospitalization of patients with psychiatric disorders (49-53).

Corroborating this knowledge, the cannabis use patterns observed in our study demonstrate that concern is warranted for the mental health of users. In our sample of patients with psychiatric disorders, the number of daily cannabis users was almost four-fold higher than that of the general population (26.5% vs. 6.0%, respectively) within a year post-legalization of cannabis in Canada (54). This finding is supported by studies reporting increased use among people with psychiatric conditions (55).

Intervention may also be necessary to hinder CUD development. Cannabis users reported considerable chronicity (on average 14 years) and presented with moderate cannabis use disorder according to DSM-5 criteria. Given that the advancement of substance use disorders occurs gradually, preventive measures should be implemented in the early stages of identified cannabis use disorders to prevent progression (56).

In our study, users of cannabis typically initiated use during adolescence (at age 15). This is a critical period of physical, psychological, and emotional development. Compared to chronic users in the general population, patients with psychiatric disorders initiated cannabis use three years earlier (23) and there is evidence that commencing cannabis use during youth increases the probability of developing a psychiatric disorder in adulthood (56-58). The onset of cannabis use by 15 years of age is associated with an increased risk of developing symptoms of schizophrenia as a young adult compared to later onset by age 18, although groups were unbalanced (56). Other studies have also demonstrated a positive relationship between age of onset of cannabis use and age of onset of psychosis (58, 59). One possibility is that use of cannabis and psychosis is related to the cumulative exposure to cannabis rather than immaturity of the adolescent

brain, as an average delay of seven to eight years till onset of psychosis was observed across all ages of cannabis use initiation (58, 59). Regardless, adolescent use of cannabis is particularly concerning as these findings suggest that an increase in adolescent cannabis use may result in an increase in young people with psychosis.

Use of cannabis by age 15 years and older has increased by 2% one year after cannabis legalization in Canada (54). The increasing use of cannabis underscores the need to prevent cannabis use in adolescents as a mitigating strategy against developing mental health concerns.

The findings of this study are noteworthy as this study examined the relationship between cannabis use and cardiometabolic risk factors, as well as cannabis use patterns post-legalization. Our work has several strengths, including quantifying cannabis amounts in grams as opposed to the number of joints, which may vary in size (15, 45). Another strength is that cannabis use patterns for this population were also presented including age of initiation, chronicity, and strains typically used. We also adjusted for potential confounders, including psychiatric diagnosis, use of antipsychotic medication, and cigarette smoking.

One limitation of this study is that we did not have data on physical activity and diet, so these variables were not controlled for in the analysis. Incorporating physical activity and diet in previous analyses was not found to alter results meaningfully in a large prospective study with similar findings to our study (6).

Another limitation was reliance on self-reported data to explore cannabis use patterns, which may introduce social desirability bias (60). However, patients who

expressed concern for confidentiality chose not to participate in the study (Figure 1). In addition, the cross-sectional design limited our ability to determine how cannabis use affected physical health, and some of these effects require longitudinal follow-up to establish their occurrence and frequency.

In conclusion, no association between cannabis use and cardiometabolic factors was found. Users demonstrated significant unemployment rates, and many had moderate cannabis use disorder. With recent legalization, increased surveillance of access to cannabis and restrictions on marketing are critical to reduce early adolescent exposure and future burden on the healthcare system. Further research into phytocannabinoid interactions, specifically elucidating the mechanisms underlying physical and mental effects is needed.

Acknowledgements

We would like to thank the patients for their participation in the study.

Data availability

The datasets generated during and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable justification.

References

1. WHO. Cannabis: World Health Organization; 2010 [updated 2010-12-07 12:45:03. Available from: https://www.who.int/substance_abuse/facts/cannabis/en/.
2. Hajizadeh M. Legalizing and regulating marijuana in Canada: review of potential economic, social, and health impacts. Int J Health Policy Manag. 2016;5(8):453-6.
3. Cunningham JA. Beliefs about cannabis at the time of legalization in Canada: results from a general population survey. Harm Reduct J. 2020;17(1):2.
4. Atakan Z. Cannabis, a complex plant: different compounds and different effects on individuals. Ther Adv Psychopharmacol. 2012;2(6):241-54.
5. Gaoni Y, Mechoulam R. Isolation, structure, and partial synthesis of an active constituent of hashish. J Am Chem Soc. 1964;86(8):1646-7.
6. Rodondi N, Pletcher MJ, Liu K, Hulley SB, Sidney S. Marijuana use, diet, body mass index, and cardiovascular risk factors (from the CARDIA study). Am J Cardiol. 2006;98(4):478-84.
7. Foltin RW, Fischman MW, Byrne MF. Effects of smoked marijuana on food intake and body weight of humans living in a residential laboratory. Appetite. 1988;11(1):1-14.
8. Smit E, Crespo CJ. Dietary intake and nutritional status of US adult marijuana users: results from the Third National Health and Nutrition Examination Survey. Public Health Nutr. 2001;4(3):781-6.
9. Hollister LE. Hunger and appetite after single doses of marihuana, alcohol, and dextroamphetamine. Clin Pharmacol Ther. 1971;12(1):44-9.
10. Beal JE, Olson R, Laubenstein L, Morales JO, Bellman P, Yangco B, et al. Dronabinol as a treatment for anorexia associated with weight loss in patients with AIDS. J Pain Symptom Manage. 1995;10(2):89-97.
11. Struwe M, Kaempfer SH, Geiger CJ, Pavia AT, Plasse TF, Shepard KV, et al. Effect of dronabinol on nutritional status in HIV infection. Ann Pharmacother. 1993;27(7-8):827-31.
12. Abrams DI, Hilton JF, Leiser RJ, Shade SB, Elbeik TA, Aweeka FT, et al. Short-term effects of cannabinoids in patients with HIV-1 infection: a randomized, placebo-controlled clinical trial. Ann Intern Med. 2003;139(4):258-66.
13. Gorter R, Seefried M, Volberding P. Dronabinol effects on weight in patients with HIV infection. Aids. 1992;6(1):127.
14. Olefsky J, Crapo PA, Ginsberg H, Reaven GM. Metabolic effects of increased caloric intake in man. Metabolism. 1975;24(4):495-503.
15. Muniyappa R, Sable S, Ouwerkerk R, Mari A, Gharib AM, Walter M, et al. Metabolic effects of chronic cannabis smoking. Diabetes Care. 2013;36(8):2415-22.
16. Penner EA, Buettner H, Mittleman MA. The impact of marijuana use on glucose, insulin, and insulin resistance among US adults. Am J Med. 2013;126(7):583-9.
17. Warren M, Frost-Pineda K, Gold M. Body mass index and marijuana use. J Addict Dis. 2005;24(3):95-100.

18. Mateo I, Pinedo A, Gomez-Beldarrain M, Basterretxea JM, Garcia-Monco JC. Recurrent stroke associated with cannabis use. J Neurol Neurosurg Psychiatry. 2005;76(3):435-7.
19. Trojak B, Leclerq S, Meille V, Khoumri C, Chauvet-Gelinier JC, Giroud M, et al. Stroke with neuropsychiatric sequelae after cannabis use in a man: a case report. J Med Case Rep. 2011;5:264.
20. Zachariah SB. Stroke after heavy marijuana smoking. Stroke. 1991;22(3):406-9.
21. Mittleman MA, Lewis RA, Maclure M, Sherwood JB, Muller JE. Triggering myocardial infarction by marijuana. Circulation. 2001;103(23):2805-9.
22. Jouanjus E, Lapeyre-Mestre M, Micallef J. Cannabis use: signal of increasing risk of serious cardiovascular disorders. J Am Heart Assoc. 2014;3(2):e000638.
23. Pinto JV, Medeiros LS, Santana da Rosa G, Santana de Oliveira CE, Crippa JAS, Passos IC, et al. The prevalence and clinical correlates of cannabis use and cannabis use disorder among patients with bipolar disorder: a systematic review with meta-analysis and meta-regression. Neurosci Biobehav Rev. 2019;101:78-84.
24. Koskinen J, Löhönen J, Koponen H, Isohanni M, Miettunen J. Rate of cannabis use disorders in clinical samples of patients with schizophrenia: a meta-analysis. Schizophr Bull. 2020;36(6):1115-30.
25. Haberstick BC, Young SE, Zeiger JS, Lessem JM, Hewitt JK, Hopfer CJ. Prevalence and correlates of alcohol and cannabis use disorders in the United States: results from the national longitudinal study of adolescent health. Drug Alcohol Depend. 2014;136:158-61.
26. Mhalla A, Bel Hadj Salah W, Mensi R, Amamou B, Messaoud A, Gassab L, et al. Lipid profile in schizophrenia: case control study. La Tunisie medicale. 2018;96(1):22-9.
27. Heald A, Pendlebury J, Anderson S, Narayan V, Guy M, Gibson M, et al. Lifestyle factors and the metabolic syndrome in schizophrenia: a cross-sectional study. Ann Gen Psychiatry. 2017;16:12.
28. Penninx BW, Milaneschi Y, Lamers F, Vogelzangs N. Understanding the somatic consequences of depression: biological mechanisms and the role of depression symptom profile. BMC Med. 2013;11:129.
29. McIntyre RS, Soczynska JK, Beyer JL, Woldeyohannes HO, Law CW, Miranda A, et al. Medical comorbidity in bipolar disorder: re-prioritizing unmet needs. Curr Opin Psychiatry. 2007;20(4):406-16.
30. Wharton S, Raiber L, Serodio KJ, Lee J, Christensen RA. Medications that cause weight gain and alternatives in Canada: a narrative review. Diabetes Metab Syndr Obes. 2018;11:427-38.
31. Bernstein JG. Induction of obesity by psychotropic drugs. Ann N Y Acad Sci. 1987;499:203-15.
32. Serretti A, Mandelli L. Antidepressants and body weight: a comprehensive review and meta-analysis. J Clin Psychiatry. 2010;71(10):1259-72.
33. Citrome L, Holt RI, Walker DJ, Hoffmann VP. Weight gain and changes in metabolic variables following olanzapine treatment in schizophrenia and bipolar disorder. Clin Drug Investig. 2011;31(7):455-82.

34. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders (DSM-5). 5th ed. Arlington, VA: American Psychiatric Publishing; 2013.
35. Mariani JJ, Brooks D, Haney M, Levin FR. Quantification and comparison of marijuana smoking practices: blunts, joints, and pipes. Drug Alcohol Depend. 2011;113(2-3):249-51.
36. Zielinski L, Bhatt M, Sanger N, Plater C, Worster A, Varenbut M, et al. Association between cannabis use and methadone maintenance treatment outcomes: an investigation into sex differences. Biol Sex Differ. 2017;8(1):1-10.
37. Gutin I. In BMI We Trust: Reframing the Body Mass Index as a Measure of Health. Social theory & health : STH. 2018;16(3):256-71.
38. IBM. IBM SPSS Statistics for Windows. 26.0 ed. Armonk, NY2019.
39. Zwillich CW, Doekel R, Hammill S, Weil JV. The effects of smoked marijuana on metabolism and respiratory control. Am Rev Respir Dis. 1978;118(5):885-91.
40. Cawthorne MA, Wargent E, Zaibi M, Stott C, Wright S. The CB-1 antagonist, delta 9 tetrahydrocannabivarin (THCV) has anti-obesity activity in dietary-induced obese (DIO) mice. 17th Annual Symposium on the Cannabinoids; Burlington, Vermont: International Cannabinoid Research Society; 2007. p. 141.
41. Alshaarawy O, Elbaz HA. Cannabis use and blood pressure levels: United States National Health and Nutrition Examination Survey, 2005-2012. J Hypertens. 2016;34(8):1507-12.
42. Le Foll B, Trigo JM, A. SK, Le Strat Y. Cannabis and 9-tetrahydrocannabinol (THC) for weight loss? Med Hypotheses. 2013;80(5):564-7.
43. Sidney S. Cardiovascular consequences of marijuana use. J Clin Pharmacol. 2002;42(S1):64s-70s.
44. Le Strat Y, Le Foll B. Obesity and cannabis use: results from 2 representative national surveys. Am J Epidemiol. 2011;174(8):929-33.
45. Bruins J, Pijnenborg MG, Bartels-Velthuis AA, Visser E, van den Heuvel ER, Bruggeman R, et al. Cannabis use in people with severe mental illness: The association with physical and mental health--a cohort study. A Pharmacotherapy Monitoring and Outcome Survey study. J Psychopharmacol. 2016;30(4):354-62.
46. Vazquez-Bourgon J, Setien-Suero E, Pilar-Cuellar F, Romero-Jimenez R, Ortiz-Garcia de la Foz V, Castro E, et al. Effect of cannabis on weight and metabolism in first-episode non-affective psychosis: results from a three-year longitudinal study. J Psychopharmacol. 2019;33(3):284-94.
47. Scheffler F, Kilian S, Chiliza B, Asmal L, Phahladira L, du Plessis S, et al. Effects of cannabis use on body mass, fasting glucose and lipids during the first 12 months of treatment in schizophrenia spectrum disorders. Schizophrenia Research. 2018;199:90-5.
48. Ramesh D, Haney M, Cooper ZD. Marijuana's dose-dependent effects in daily marijuana smokers. Exp Clin Psychopharmacol. 2013;21(4):287-93.
49. Grech A, Van Os J, Jones PB, Lewis SW, Murray RM. Cannabis use and outcome of recent onset psychosis. Eur Psychiatry. 2005;20(4):349-53.
50. Linszen DH, Dingemans PM, Lenior ME. Cannabis abuse and the course of recent-onset schizophrenic disorders. Arch Gen Psychiatry. 2020;51(4):273-9.

51. Isaac M, Holloway F. Is cannabis an anti-antipsychotic? The experience in psychiatric intensive care. Hum Psychopharmacol. 2005;20(3):207-10.
52. Bahorik AL, Leibowitz A, Sterling SA, Travis A, Weisner C, Satre DD. Patterns of marijuana use among psychiatry patients with depression and its impact on recovery. J Affect Disord. 2017;213:168-71.
53. Compton WM, Han B, Jones CM, Blanco C, Hughes A. Marijuana use and use disorders in adults in the USA, 2002-14: analysis of annual cross-sectional surveys. Lancet Psychiatry. 2016;3(10):954-64.
54. Rotermann M. What has changed since cannabis was legalized? Health Rep. 2020;31(2):11-20.
55. Lev-Ran S, Le Foll B, McKenzie K, George TP, Rehm J. Cannabis use and cannabis use disorders among individuals with mental illness. Compr Psychiatry. 2013;54(6):589-98.
56. Arseneault L, Cannon M, Poulton R, Murray R, Caspi A, Moffitt TE. Cannabis use in adolescence and risk for adult psychosis: longitudinal prospective study. BMJ. 2002;325(7374):1212-3.
57. Andreasson S, Allebeck P, Engstrom A, Rydberg U. Cannabis and schizophrenia. A longitudinal study of Swedish conscripts. Lancet. 1987;2(8574):1483-6.
58. Galvez-Buccollini JA, Proal AC, Tomaselli V, Trachtenberg M, Coconcea C, Chun J, et al. Association between age at onset of psychosis and age at onset of cannabis use in non-affective psychosis. Schizophr Res. 2012;139(1-3):157-60.
59. Stefanis NC, Dragovic M, Power BD, Jablensky A, Castle D, Morgan VA. Age at initiation of cannabis use predicts age at onset of psychosis: the 7- to 8-year trend. Schizophr Bull. 2013;39(2):251-4.
60. Hammond D, Goodman S, Wadsworth E, Rynard V, Boudreau C, Hall W. Evaluating the impacts of cannabis legalization: The International Cannabis Policy Study. Int J Drug Policy. 2020;77:102698.

Table 1. Sociodemographic and clinical characteristics of users and non-users of cannabis in patients with psychiatric disorders.

	Users	Non-users
	n = 79	*n* = 121
Age, years, mean (SD)	34.2 (11.9)	40.4 (14.9)
Sex, *n* (% male)	45 (57.0)	69 (57.0)
Ethnicity, *n* (% European)	52 (65.8)	89 (73.6)
Highest level of education achieved, *n* (%)		
High school or less	49 (62.0)	59 (48.8)
Post-secondary education	30 (37.9)	62 (51.2)
Marital status, *n* (% never married)	50 (63.3)	73 (60.3)
Employment, *n* (% unemployed)	62 (78.4)	87 (71.9)
ODSP income support, *n* (%)	32 (40.5)	29 (24.0)
Diagnosis, *n* (%)		
Neurodevelopmental disorders	0 (0.0)	2 (1.7)
Schizophrenia spectrum and other psychotic disorders	16 (20.2)	18 (14.9)
Bipolar and related disorders	20 (25.3)	28 (23.1)
Depressive disorders	10 (12.7)	48 (39.7)
Anxiety disorders	10 (12.7)	8 (6.6)
Personality disorders	11 (13.9)	12 (9.9)
Substance-related and addictive disorders	6 (7.6)	4 (3.3)
Other mental disorders	6 (7.6)	1 (0.8)
Use of antipsychotic medications, *n* (%)		
Typical antipsychotic medications	6 (7.6)	9 (7.4)
Atypical antipsychotic medications	44 (55.7)	58 (47.9)
Both typical and atypical medications	10 (12.6)	15 (12.4)
No antipsychotic medications	15 (19.0)	29 (24.0)
Unspecified	4 (5.1)	10 (8.3)
Smoking status, *n* (% yes)	55 (69.6)	50 (41.3)
No. of cigarettes smoked per day, mean (SD)	9.7 (11.0)	5.6 (9.6)
Age of smoking initiation, mean (SD)	16.0 (5.8)	18.0 (8.2)
BMI (kg/m^2), mean (SD) (n = 52, 88)	26.7 (6.8)	28.4 (6.7)
Blood pressure, mean (SD) (n = 75, 120)		
Systolic blood pressure (mmHg)	121.9 (11.6)	126.8 (16.8)
Diastolic blood pressure (mmHg)	78.1 (8.7)	79.4 (9.2)

Abbreviations: SD = standard deviation; ODSP = Ontario Disability Support Program; BMI = body mass index.

Table 2. Laboratory values of users and non-users of cannabis in patients with psychiatric disorders.

Laboratory values[a]	Users	Non-users
Total cholesterol (mmol/L) (n = 60, 103) Normal: < 5.2 mmol/L	4.7 (1.1)	4.8 (1.1)
HDL-C (mmol/L) (n = 60, 102) Normal: males: ≥ 1.0 mmol/L; females: ≥ 1.3	1.3 (0.5)	1.3 (0.4)
LDL-C (mmol/L) (n = 58, 99) Normal: < 3.0 mmol/L	2.7 (0.9)	2.8 (0.9)
Triglycerides (mmol/L) (n = 59, 99) Normal: < 1.7 mmol/L	1.5 (0.7)	1.7 (0.8)
HbA1c (%) (n = 53, 100) Normal: < 6.0 %	5.4 (0.7)	5.5 (1.1)

[a]The number of users and non-users contributing data (*n* = users, non- users).
Abbreviations: HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; HbA1c = Hemoglobin A1c.

Table 3. Regression analysis for the association between cannabis use status and cardiometabolic risk factors in patients with psychiatric conditions[a]

Outcomes	Difference[b] (95% CI)	*P* value[c]
Body mass index (kg/m^2)	-1.29 (-3.88, 1.30)	0.33
Systolic blood pressure (mmHg)	-3.30 (-8.14, 1.53)	0.18
Diastolic blood pressure (mmHg)	-0.64 (-3.54, 2.26)	0.67
Total cholesterol (mmol/L)	0.04 (-0.33, 0.41)	0.84
Triglycerides (mmol/L)	-0.13 (-0.42, 0.16)	0.39
HDL-C (mmol/L)	-0.02 (-0.18, 0.14)	0.80
LDL-C (mmol/L)	0.06 (-0.27, 0.38)	0.72
HbA1c (%)	0.05 (-0.31, 0.41)	0.78

[a]All analyses adjusted for age, sex, psychiatric diagnoses, use of antipsychotic medications and number of cigarettes used per day.
[b](User – Non-user)
[c]A difference of P < 0.006 was considered statistically significant.
Abbreviations: CI = confidence interval; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; HbA1c = Hemoglobin A1c.

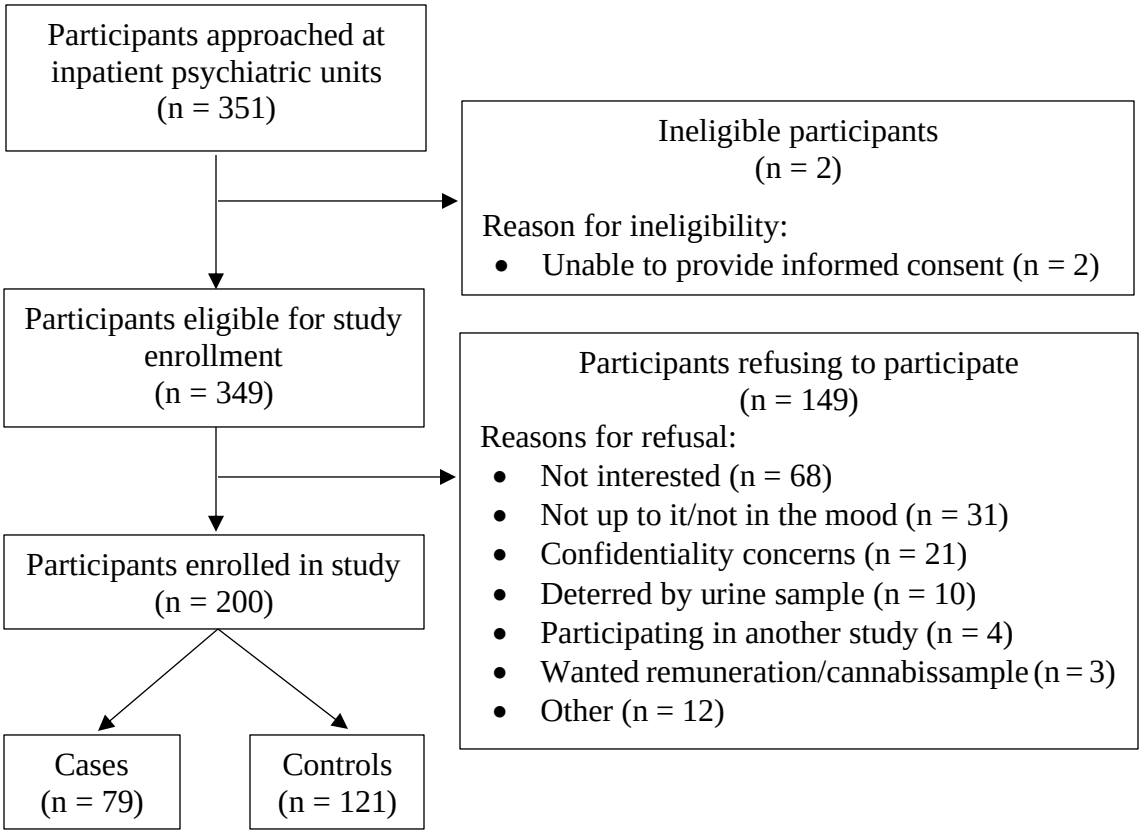
Table 4. Cannabis use patterns among users with psychiatric disorders.

Cannabis use patterns	Mean (SD)
Age of cannabis use initiation (n = 79)	15.2 (3.5)
Minimum amount of cannabis used per day (g) (n = 74)	1.6 (1.8)
Number of years of cannabis use (n = 78)	13.5 (11.0)
Amount spent on cannabis per week (in dollars) (n = 77)	65.5 (85.8)
Cannabis use disorder score (n = 79)	4.3 (3.4)
Cannabis use patterns	***n*** **(%)**
Cannabis use disorder	57 (72.2)
Cannabis use frequency	
Everyday	53 (67.1)
Every other day	5 (6.3)
1-3 times per week	10 (12.6)
2-3 times per month	11 (13.9)
Method(s) of cannabis consumption[a]	
Joint	59 (74.7)
Bong	28 (35.4)
Bowl	12 (15.2)
Ingestion	11 (13.9)
One-hitter	2 (2.5)
Oil	8 (10.1)
Other	15 (19.0)
Strains or brands of cannabis used[a]	
Indica	27 (34.2)
Sativa	20 (25.3)
Hybrid	11 (13.9)
CBD oil	2 (2.5)
Concentrates	3 (3.8)
Hash	1 (1.3)
Kush variant	9 (11.4)
Butane honey oil	1 (1.3)
White widow unk	1 (1.3)
Death star	1 (1.3)
Ice cream	1 (1.3)
Trainwreck	1 (1.3)
Green crack	1 (1.3)
Cookies and Creme	1 (1.3)
Mota edibles	1 (1.3)
Avi-Dekel	1 (1.3)
Midnight	1 (1.3)
Trutiva	1 (1.3)

Purple urkle	1 (1.3)
Zeus	1 (1.3)
Equiposa	1 (1.3)

[a]Multiple responses were permitted.

Figure 1. Flow diagram for Cannabis and Physical Health study recruitment



CHAPTER 3: DISCUSSION & CONCLUSIONS

The global increase in cannabis use is in parallel to a global epidemic of type 2 diabetes and cardiovascular disease (71), and the latter conditions continue to be some of the most common causes of death worldwide (72). We specifically examined a subset of adult patients with psychiatric conditions for the impact of cannabis use on their cardiometabolic health. We determined that in this cross-sectional design, the users had a similar cardiometabolic profile to non-users.

Despite the absence of an association between cannabis use and cardiometabolic risk factors, we determined that cannabis use was concerning in this population, given the presence of pre-existing psychiatric diagnoses. In our sample of patients with psychiatric conditions, use patterns revealed increased frequency and early life onset of cannabis use. When compared to the general population, these findings indicate that these patients are more vulnerable to adverse mental health impacts of cannabis use due to the higher proportion of daily users and comparatively earlier age of onset. Most users also had a moderate cannabis use disorder and long exposure to cannabis. High chronicity and moderate cannabis use disorder in our sample suggest that prolonged use may be related to an increased severity of cannabis use disorder, and efforts should be made to impede progression in patients with psychiatric conditions. Finally, cannabis users consumed moderate amounts of cannabis, primarily consumed *indica* and *sativa* strains, and joints were the most common method of consumption.

Our findings expand the limited body of evidence examining the impact of cannabis use on cardiometabolic health in patients with psychiatric conditions. We included patients with varying psychiatric diagnoses, and adjusted for potential confounders, including psychiatric diagnoses, use of antipsychotic medications, and cigarette smoking. We also quantified cannabis amounts using grams and explored use patterns post-legalization. However, our results are limited by self-reporting for cannabis use patterns, lack of data on physical activity and diet, and the cross-sectional design of our study.

In terms of future areas of research, long-term and larger studies are needed to examine the effects of cannabis use on patients with different psychiatric disorders. A larger sample size will allow for subgroup analyses in this population and a longitudinal study design will permit the assessment of changes in cardiometabolic risk factors with cannabis use. Future studies should include data on important contributors to cardiometabolic health, particularly physical activity and diet, and also quantify cannabis amounts to strengthen conclusions made about cannabis use. Research is also needed to determine whether methods of cannabis consumption differentially impact cardiometabolic health.

More work needs to be done to understand and characterize the isolated phytocannabinoids in cannabis. A better understanding of its individual components will provide greater knowledge of the effects of cannabis on the body which is presently clouded by many unknowns and much variability.

REFERENCES

1. Zhou Y, Falenta K, Lalli G. Endocannabinoid signalling in neuronal migration. Int J Biochem Cell Biol. 2014;47:104-8.
2. Abood ME, Martin BR. Molecular neurobiology of the cannabinoid receptor. Int Rev Neurobiol. 1996;39:197-221.
3. Piomelli D. The molecular logic of endocannabinoid signalling. Nat Rev Neurosci. 2003;4(11):873-84.
4. Gaoni Y, Mechoulam R. Isolation, structure, and partial synthesis of an active constituent of hashish. J Am Chem Soc. 1964;86(8):1646-7.
5. Devane WA, Dysarz FA, 3rd, Johnson MR, Melvin LS, Howlett AC. Determination and characterization of a cannabinoid receptor in rat brain. Mol Pharmacol. 1988;34(5):605-13.
6. Matsuda LA, Lolait SJ, Brownstein MJ, Young AC, Bonner TI. Structure of a cannabinoid receptor and functional expression of the cloned cDNA. Nature. 1990;346(6284):561-4.
7. Munro S, Thomas KL, Abu-Shaar M. Molecular characterization of a peripheral receptor for cannabinoids. Nature. 1993;365(6441):61-5.
8. Devane WA, Hanus L, Breuer A, Pertwee RG, Stevenson LA, Griffin G, et al. Isolation and structure of a brain constituent that binds to the cannabinoid receptor. Science. 1992;258(5090):1946-9.
9. Mechoulam R, Ben-Shabat S, Hanus L, Ligumsky M, Kaminski NE, Schatz AR, et al. Identification of an endogenous 2-monoglyceride, present in canine gut, that binds to cannabinoid receptors. Biochem Pharmacol. 1995;50(1):83-90.
10. Sugiura T, Kondo S, Sukagawa A, Nakane S, Shinoda A, Itoh K, et al. 2-Arachidonoylglycerol: a possible endogenous cannabinoid receptor ligand in brain. Biochem Biophys Res Commun. 1995;215(1):89-97.
11. Mackie K. Distribution of cannabinoid receptors in the central and peripheral nervous system. Handb Exp Pharmacol. 2005(168):299-325.
12. Walter L, Franklin A, Witting A, Wade C, Xie Y, Kunos G, et al. Nonpsychotropic cannabinoid receptors regulate microglial cell migration. The Journal of neuroscience : the official journal of the Society for Neuroscience. 2003;23(4):1398-405.
13. Jorda MA, Verbakel SE, Valk PJ, Vankan-Berkhoudt YV, Maccarrone M, Finazzi-Agro A, et al. Hematopoietic cells expressing the peripheral cannabinoid receptor migrate in response to the endocannabinoid 2-arachidonoylglycerol. Blood. 2002;99(8):2786-93.
14. Pagotto U, Marsicano G, Cota D, Lutz B, Pasquali R. The emerging role of the endocannabinoid system in endocrine regulation and energy balance. Endocr Rev. 2006;27(1):73-100.
15. Pacher P, Batkai S, Kunos G. The endocannabinoid system as an emerging target of pharmacotherapy. Pharmacol Rev. 2006;58(3):389-462.

16. Simon V, Cota D. MECHANISMS IN ENDOCRINOLOGY: Endocannabinoids and metabolism: past, present and future. Eur J Endocrinol. 2017;176(6):R309-r24.
17. Nagappan A, Shin J, Jung MH. Role of Cannabinoid Receptor Type 1 in Insulin Resistance and Its Biological Implications. International journal of molecular sciences. 2019;20(9):2109.
18. Maccarrone M, Guzman M, Mackie K, Doherty P, Harkany T. Programming of neural cells by (endo)cannabinoids: from physiological rules to emerging therapies. Nat Rev Neurosci. 2014;15(12):786-801.
19. Wilson RI, Nicoll RA. Endocannabinoid signaling in the brain. Science. 2002;296(5568):678-82.
20. Gulyas AI, Cravatt BF, Bracey MH, Dinh TP, Piomelli D, Boscia F, et al. Segregation of two endocannabinoid-hydrolyzing enzymes into pre- and postsynaptic compartments in the rat hippocampus, cerebellum and amygdala. Eur J Neurosci. 2004;20(2):441-58.
21. Williams EJ, Walsh FS, Doherty P. The FGF receptor uses the endocannabinoid signaling system to couple to an axonal growth response. J Cell Biol. 2003;160(4):481-6.
22. Aguado T, Palazuelos J, Monory K, Stella N, Cravatt B, Lutz B, et al. The endocannabinoid system promotes astroglial differentiation by acting on neural progenitor cells. J Neurosci. 2006;26(5):1551-61.
23. Berghuis P, Rajnicek AM, Morozov YM, Ross RA, Mulder J, Urban GM, et al. Hardwiring the brain: endocannabinoids shape neuronal connectivity. Science. 2007;316(5828):1212-6.
24. Pertwee RG. Cannabinoid pharmacology: the first 66 years. British journal of pharmacology. 2006;147 Suppl 1(Suppl 1):S163-S71.
25. Volkow ND, Baler RD, Compton WM, Weiss SRB. Adverse health effects of marijuana use. The New England journal of medicine. 2014;370(23):2219-27.
26. Zalesky A, Solowij N, Yucel M, Lubman DI, Takagi M, Harding IH, et al. Effect of long-term cannabis use on axonal fibre connectivity. Brain. 2012;135(Pt 7):2245-55.
27. Meier MH, Caspi A, Ambler A, Harrington H, Houts R, Keefe RS, et al. Persistent cannabis users show neuropsychological decline from childhood to midlife. Proc Natl Acad Sci U S A. 2012;109(40):E2657-64.
28. Bermudez-Silva FJ, Suarez Perez J, Nadal A, Rodriguez de Fonseca F. The role of the pancreatic endocannabinoid system in glucose metabolism. Best Pract Res Clin Endocrinol Metab. 2009;23(1):87-102.
29. Nomura DK, Morrison BE, Blankman JL, Long JZ, Kinsey SG, Marcondes MC, et al. Endocannabinoid hydrolysis generates brain prostaglandins that promote neuroinflammation. Science. 2011;334(6057):809-13.
30. Lu HC, Mackie K. An Introduction to the Endogenous Cannabinoid System. Biol Psychiatry. 2016;79(7):516-25.
31. Schwabe RF. Endocannabinoids promote hepatic lipogenesis and steatosis through CB1 receptors. Hepatology. 2005;42(4):959-61.

32. Cota D, Marsicano G, Tschop M, Grubler Y, Flachskamm C, Schubert M, et al. The endogenous cannabinoid system affects energy balance via central orexigenic drive and peripheral lipogenesis. J Clin Invest. 2003;112(3):423-31.
33. Jamshidi N, Taylor DA. Anandamide administration into the ventromedial hypothalamus stimulates appetite in rats. Br J Pharmacol. 2001;134(6):1151-4.
34. Hao S, Avraham Y, Mechoulam R, Berry EM. Low dose anandamide affects food intake, cognitive function, neurotransmitter and corticosterone levels in diet-restricted mice. Eur J Pharmacol. 2000;392(3):147-56.
35. Shearman LP, Rosko KM, Fleischer R, Wang J, Xu S, Tong XS, et al. Antidepressant-like and anorectic effects of the cannabinoid CB1 receptor inverse agonist AM251 in mice. Behav Pharmacol. 2003;14(8):573-82.
36. Di Marzo V, Goparaju SK, Wang L, Liu J, Batkai S, Jarai Z, et al. Leptin-regulated endocannabinoids are involved in maintaining food intake. Nature. 2001;410(6830):822-5.
37. Poncelet M, Maruani J, Calassi R, Soubrie P. Overeating, alcohol and sucrose consumption decrease in CB1 receptor deleted mice. Neurosci Lett. 2003;343(3):216-8.
38. Osei-Hyiaman D, Liu J, Zhou L, Godlewski G, Harvey-White J, Jeong WI, et al. Hepatic CB1 receptor is required for development of diet-induced steatosis, dyslipidemia, and insulin and leptin resistance in mice. J Clin Invest. 2008;118(9):3160-9.
39. Osei-Hyiaman D, DePetrillo M, Pacher P, Liu J, Radaeva S, Bátkai S, et al. Endocannabinoid activation at hepatic CB1 receptors stimulates fatty acid synthesis and contributes to diet-induced obesity. The Journal of clinical investigation. 2005;115(5):1298-305.
40. Postic C, Girard J. Contribution of de novo fatty acid synthesis to hepatic steatosis and insulin resistance: lessons from genetically engineered mice. The Journal of clinical investigation. 2008;118(3):829-38.
41. Tharp WG, Lee YH, Maple RL, Pratley RE. The cannabinoid CB1 receptor is expressed in pancreatic delta-cells. Biochem Biophys Res Commun. 2008;372(4):595-600.
42. Bermudez-Silva FJ, Suarez J, Baixeras E, Cobo N, Bautista D, Cuesta-Munoz AL, et al. Presence of functional cannabinoid receptors in human endocrine pancreas. Diabetologia. 2008;51(3):476-87.
43. Kim W, Doyle ME, Liu Z, Lao Q, Shin YK, Carlson OD, et al. Cannabinoids inhibit insulin receptor signaling in pancreatic beta-cells. Diabetes. 2011;60(4):1198-209.
44. Gonzalez-Mariscal I, Krzysik-Walker SM, Kim W, Rouse M, Egan JM. Blockade of cannabinoid 1 receptor improves GLP-1R mediated insulin secretion in mice. Mol Cell Endocrinol. 2016;423:1-10.
45. Gonzalez-Mariscal I, Krzysik-Walker SM, Doyle ME, Liu QR, Cimbro R, Santa-Cruz Calvo S, et al. Human CB1 Receptor Isoforms, present in Hepatocytes and beta-cells, are Involved in Regulating Metabolism. Sci Rep. 2016;6:33302.
46. Tengholm A, Gylfe E. cAMP signalling in insulin and glucagon secretion. Diabetes Obes Metab. 2017;19 Suppl 1:42-53.

47. Esposito I, Proto MC, Gazzerro P, Laezza C, Miele C, Alberobello AT, et al. The cannabinoid CB1 receptor antagonist rimonabant stimulates 2-deoxyglucose uptake in skeletal muscle cells by regulating the expression of phosphatidylinositol-3-kinase. Mol Pharmacol. 2008;74(6):1678-86.
48. Liu YL, Connoley IP, Wilson CA, Stock MJ. Effects of the cannabinoid CB1 receptor antagonist SR141716 on oxygen consumption and soleus muscle glucose uptake in Lep(ob)/Lep(ob) mice. Int J Obes (Lond). 2005;29(2):183-7.
49. Eckardt K, Sell H, Taube A, Koenen M, Platzbecker B, Cramer A, et al. Cannabinoid type 1 receptors in human skeletal muscle cells participate in the negative crosstalk between fat and muscle. Diabetologia. 2009;52(4):664-74.
50. Jaiswal N, Gavin MG, Quinn WJ, 3rd, Luongo TS, Gelfer RG, Baur JA, et al. The role of skeletal muscle Akt in the regulation of muscle mass and glucose homeostasis. Mol Metab. 2019;28:1-13.
51. Greenberg I, Kuehnle J, Mendelson JH, Bernstein JG. Effects of marihuana use on body weight and caloric intake in humans. Psychopharmacology (Berl). 1976;49(1):79-84.
52. Volicer L, Stelly M, Morris J, McLaughlin J, Volicer BJ. Effects of dronabinol on anorexia and disturbed behavior in patients with Alzheimer's disease. Int J Geriatr Psychiatry. 1997;12(9):913-9.
53. Andries A, Frystyk J, Flyvbjerg A, Stoving RK. Dronabinol in severe, enduring anorexia nervosa: a randomized controlled trial. Int J Eat Disord. 2014;47(1):18-23.
54. Olefsky J, Crapo PA, Ginsberg H, Reaven GM. Metabolic effects of increased caloric intake in man. Metabolism. 1975;24(4):495-503.
55. Larsson SC, Back M, Rees JMB, Mason AM, Burgess S. Body mass index and body composition in relation to 14 cardiovascular conditions in UK Biobank: a Mendelian randomization study. Eur Heart J. 2020;41(2):221-6.
56. Field AE, Coakley EH, Must A, Spadano JL, Laird N, Dietz WH, et al. Impact of overweight on the risk of developing common chronic diseases during a 10-year period. Arch Intern Med. 2001;161(13):1581-6.
57. Ohlson LO, Larsson B, Svardsudd K, Welin L, Eriksson H, Wilhelmsen L, et al. The influence of body fat distribution on the incidence of diabetes mellitus. 13.5 years of follow-up of the participants in the study of men born in 1913. Diabetes. 1985;34(10):1055-8.
58. Chan JM, Rimm EB, Colditz GA, Stampfer MJ, Willett WC. Obesity, fat distribution, and weight gain as risk factors for clinical diabetes in men. Diabetes Care. 1994;17(9):961-9.
59. United Nations Office on Drugs and Crime. World Drug Report 2019. Vienna; 2019.
60. Government of Canada. About cannabis 2019 [Available from: https://www.canada.ca/en/health-canada/services/drugs-medication/cannabis/about.html.
61. Cunningham JA. Beliefs about cannabis at the time of legalization in Canada: results from a general population survey. Harm Reduct J. 2020;17(1):2.

62. Green B, Young R, Kavanagh D. Cannabis use and misuse prevalence among people with psychosis. Br J Psychiatry. 2005;187:306-13.
63. Mateo I, Pinedo A, Gomez-Beldarrain M, Basterretxea JM, Garcia-Monco JC. Recurrent stroke associated with cannabis use. J Neurol Neurosurg Psychiatry. 2005;76(3):435-7.
64. Trojak B, Leclerq S, Meille V, Khoumri C, Chauvet-Gelinier JC, Giroud M, et al. Stroke with neuropsychiatric sequelae after cannabis use in a man: a case report. J Med Case Rep. 2011;5:264.
65. Zachariah SB. Stroke after heavy marijuana smoking. Stroke. 1991;22(3):406-9.
66. Penner EA, Buettner H, Mittleman MA. The impact of marijuana use on glucose, insulin, and insulin resistance among US adults. Am J Med. 2013;126(7):583-9.
67. Warren M, Frost-Pineda K, Gold M. Body mass index and marijuana use. J Addict Dis. 2005;24(3):95-100.
68. Rodondi N, Pletcher MJ, Liu K, Hulley SB, Sidney S. Marijuana use, diet, body mass index, and cardiovascular risk factors (from the CARDIA study). Am J Cardiol. 2006;98(4):478-84.
69. Bruins J, Pijnenborg MG, Bartels-Velthuis AA, Visser E, van den Heuvel ER, Bruggeman R, et al. Cannabis use in people with severe mental illness: the association with physical and mental health--a cohort study. A Pharmacotherapy Monitoring and Outcome Survey study. J Psychopharmacol. 2016;30(4):354-62.
70. Vazquez-Bourgon J, Setien-Suero E, Pilar-Cuellar F, Romero-Jimenez R, Ortiz-Garcia de la Foz V, Castro E, et al. Effect of cannabis on weight and metabolism in first-episode non-affective psychosis: results from a three-year longitudinal study. J Psychopharmacol. 2019;33(3):284-94.
71. Saeedi P, Petersohn I, Salpea P, Malanda B, Karuranga S, Unwin N, et al. Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: Results from the International Diabetes Federation Diabetes Atlas, 9(th) edition. Diabetes Res Clin Pract. 2019;157:107843.
72. Roth GA, Johnson C, Abajobir A, Abd-Allah F, Abera SF, Abyu G, et al. Global, Regional, and National Burden of Cardiovascular Diseases for 10 Causes, 1990 to 2015. Journal of the American College of Cardiology. 2017;70(1):1-25.