Université de Montréal

Le cannabis, le tabac et le changement d'adiposité chez les jeunes hommes et femmes : une étude longitudinale 2005-2012

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Ce mémoire intitulé :

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a été évalué par un jury composé des personnes suivantes :
Sylvana Côté, président-rapporteur
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RÉSUMÉ

Exposé de la situation : Des études menées sur les animaux démontrent que le système endocannabinoide est important dans le maintien de l'homéostasie de l'énergie et que les effets de sa modulation sont différents selon le sexe et l'exposition à la nicotine. Deux études longitudinales ont étudié l'association entre l'usage du cannabis (UC) et le changement de poids et ont obtenus des résultats contradictoires. L'objectif de ce mémoire est de décrire la modification de l'association entre l'UC et le changement de poids par la cigarette chez les jeunes hommes et femmes.

Méthodes : Des donnés de 271 hommes et 319 femmes ont été obtenues dans le cadre de l'étude NICO, une cohorte prospective (1999-2013). L'indice de masse corporelle (IMC) et la circonférence de taille (CT) ont été mesurés à l'âge de 17 et 25 ans. L'UC dans la dernière année et de cigarette dans les derniers trois mois ont été auto-rapportées à 21 ans. Les associations entre l'UC et le changement d'IMC et de CT ont été modélisées dans une régression polynomiale stratifiée par sexe avec ajustement pour l'activité physique, la sédentarité et la consommation d'alcool.

Résultats : Uniquement, chez les hommes, l'interaction de l'UC et cigarettes était statistiquement significative dans le model de changement IMC ($p=0.004$) et celui de changement de CT ($p=0.043$). L'UC était associé au changement d'adiposité dans une association en forme de U chez les homes non-fumeurs et chez les femmes, et dans une association en forme de U-inversé chez les hommes fumeurs.

Conclusion : La cigarette semble modifier l'effet du cannabis sur le changement d'IMC et CT chez les hommes, mais pas chez les femme.

Mots clés : Système endocannabinoide, cannabis, cigarette, obésité, modification d'effet

ABSTRACT

Background: Animal studies suggest that the endocannabinoid system is a regulator of energy homeostasis, whose effects are modified by sex and nicotine. Two studies in humans have examined the association between cannabis use and change in adiposity, and obtained conflicting results. This thesis aimed to determine if the association between cannabis use and change in adiposity is modified by cigarette smoking in young adults.

Methods: Data were available for 271 males and 319 females participating in the Nicotine Dependence In Teens study, a prospective cohort investigation (1999-2013). Body mass index (BMI) and waist circumference (WC) were measured at ages 17 and 25 years. Self-report data on past-year cannabis use and past three-month cigarette smoking were collected at age 21 years. Modification of the association between cannabis use and change in adiposity by cigarette smoking was tested separately in each sex, in polynomial linear regression models controlling for physical activity and sedentary behavior in both sexes, and alcohol use in males only.

Results: In males only, the interaction between cannabis use and cigarette smoking was statistically significant in both the model for change in BMI ($p=0.004$) and the model for change in WC ($p=0.043$). Cannabis use was associated with change in adiposity in a U-shaped form in females and in non smoking males, and in an inverted U-shaped association in males who smoked more than 10 cigarettes per day.

Conclusion: Smoking cigarettes appears to attenuate the association between cannabis use and change in adiposity in young men, but not in young women.

Key words: Endocannabinoid system, cannabis, cigarette, obesity, effect modification

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ABBREVIATIONS

2-AG	2-arachidonoylglycerol
AEA	Arachidonylethanolamide
ARC	Arcuate
BMI	Body mass index
CARDIA	Coronary Artery Risk Development in Young Adults
CNS	Central nervous system
CRH	Corticotropin-releasing hormone
ECS	Endocannabinoide system
FAAH	Fatty acid amide hydrolase
MGL	Monoacylglycerol lipase
NCSR	National Co-morbidity Survey–Replication
NDIT	Nicotine Dependence in Teens
NESARC	National Epidemiologic Survey on Alcohol and Related Conditions
NHANES III	Third National Health and Nutrition Examination Survey
NPY	Neuropeptide Y
POMC	Pro-opiomelanocortin
PVN	Paraventricular nucleus
SES	Socio-economic status
THC	Delta-9-tetrahydrocannabinol
UC	Usage du cannabis
VIF	Variance inflation factor
WC	Waist circumference
WHO	World Health Organization

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Chapter 1: Introduction

The ongoing obesity epidemic is of considerable concern worldwide. In Canada, 62% of the population is overweight or obese and the healthcare burden associated with overweight is estimated at $4.3 billion annually in direct and indirect costs (1, 2). These conditions are associated with numerous health problems including diabetes and cardiovascular disease (3).

Extensive research has identified a variety of risk factors for excess body weight including sedentary behavior, physical inactivity, poor diet, and alcohol use, all of which have been targeted for preventive intervention (4-7). One of the targets of pharmaceutical weight loss interventions is the endocannabinoid system (ECS) (8). The ECS consists of several endogenous ligands called endocannabinoids, as well as many receptors that are found throughout the body including on cells in the central nervous system, the gastrointestinal tract, the liver, adipose tissue, the endocrine pancreas, immune and hepatic cells and skeletal muscle cells (9). The ECS is implicated in a plethora of physiological pathways through its signaling molecule and receptors, which include the cannabinoid-1 (CB_1) and cannabinoid-2 (CB_2) receptors (9).

Because of interaction with the sex hormones, ECS action differs according to sex at the cellular level as well as at the endocrine level (10-12). The homeostatic effects of the ECS are more extreme in men, while its effects on mood, particularly anxiety, are more extreme in women (10). Many synthetic cannabinoids have been created for their clinical potential to decrease weight, modulate pain, and decrease

nausea, and pharmacological studies continue to explore the potential of the ECS (13, 14).

Of particular interest in this thesis is the role of the ECS in the maintenance of energy homeostasis through regulation of processes including appetite, lipogenesis and glucose uptake (14). The synthetic cannabinoid, rimonabant, was created to promote weight loss by acting antagonistically on the CB_1 and CB_2 receptors and down-regulating the ECS (13, 15). When taken regularly, rimonabant resulted in sustained weight loss independent of diet in obese patients, particularly among men, and interestingly, facilitated smoking cessation (12, 15). However, its psychiatric side effects prevented its introduction to the market. The decrease in weight resulting from inactivation of the CB_1 receptor by antagonists underscores the importance of the ECS in energy homeostasis. In fact, the ECS has an impact on virtually every aspect of the metabolic syndrome (16).

Cannabis is the most widely used illicit drug in the world (although it is not illicit in every country) with an estimated 125 to 203 million users in 2009 (17). The natural cannabinoid that first led to the identification of the CB_1 receptor, was delta-9-tetrahydrocannabinol (THC), the active component of the *cannabis sativa* plant, which acts agonistically on the CB_1 receptor (18). Its immediate effect on appetite is well known and synthetic derivatives of THC are used for their orexigenic effect in patients suffering from cancer-related anorexia and acquired immune deficiency syndrome (AIDS) (14, 16). When used recreationally, cannabis is smoked and often co-used or used simultaneously with tobacco (19). Among U.S. cannabis users, 90% reported having been a cigarette smoker (19). Human and animal studies examining

the joint effects of cigarette and cannabis use have identified cigarette smoking as an important effect modifier of the action of THC on the ECS (20). Given that cannabis stimulates the ECS and over-activation of the ECS is observed in overweight and obese individuals, it is possible that cannabis use leads to weight gain, but that this effect is modified by cigarette smoking.

To date, epidemiological studies that report on the association between cannabis use and weight are inconclusive (4, 21-25). However, most of these studies did not consider sex differences and none examined possible effect modification by cigarette smoking. In this current study, we investigated the association between cannabis use and weight change longitudinally and we tested if the association is moderated by cigarette smoking. Because the literature suggests that the association of interest may be substantively different in males and females, we investigated these issues in males and females separately.

Chapter 2: Literature Review

2.1. The biological framework of this study: the endocannabinoid system

2.1.1. Components of the endocannabinoid system

The ECS is a regulatory system formed of cannabinoid receptors, endocannabinoids and enzymes for their synthesis and inactivation (16). Among many receptors in the ECS, are two G-protein coupled receptors, CB_1 and CB_2 (8). The initial discovery of the ECS was made when the CB_1 receptor was identified as the receptor activated by delta-9-tetrahydrocannabinol (THC), the active ingredient most highly present in cannabis (18). CB_1 receptors are primarily located in the central nervous system (CNS) in the hypothalamus, the brainstem, the cerebral cortex and the mesolimbic dopaminergic system (16). These areas of the brain are responsible for energy regulation, feeding behaviors and reward circuits. CB_1 receptors have also been found in peripheral tissue including in the gastrointestinal tract, liver, adipose tissue, endocrine pancreas and skeletal muscles (9, 16). CB_2 receptors have been discovered in peripheral tissue including adipose tissue, skeletal muscle and the endocrine pancreas, where they act at the level of immune and hematopoietic cells to modulate the immune response (8). They are also located in the CNS where they act on cell proliferation, although their role remains controversial (26).

CB_1 and CB_2 receptors are activated by endogenous ligands called endocannabinoids. Since endocannabinoids are lipophilic, they are not stored in vesicles, but are formed on demand by the cell from phospholipid membrane precursors. Once released, these molecules act locally on the cell that produced them

or its neighboring cells. The two most common endocannabinoids are arachidonylethanolamide (anandamide, AEA), and 2-arachidonoylglycerol (2-AG) (9). Once bound to their receptors, the signaling molecules are enzymatically degraded within the cell by catabolic enzymes such as fatty acid amide hydrolase (FAAH) and monoacylglycerol lipase (MGL) (27). Multiple enzymes in complex cascades are involved in the synthesis and degradation of endocannabinoids. Adding to the complexity of these anabolic and catabolic cascades are enzymes that alter endocannabinoid signaling by enhancing reuptake or inhibiting degradation, thus modulating the intensity of endocannabinoid signaling (16).

2.1.2. Role in energy homeostasis

The multiple possible regulatory points in the ECS make it ideal for homeostatic control. Its activity can be altered or fine-tuned before, during or after synthesis and degradation of endocannabinoids and its efficiency can be modified through the density of its receptors and the creation of enhancing and inhibiting molecules. The widespread presence of the ECS throughout the human body and its extreme flexibility suggest an important role in maintenance of the homeostasis of many physiological processes. The ECS is implicated in suppression of aversive memory, motivation to eat, perceived palatability of food, creation of a stress response and emotional regulation through its receptors in the CNS (9, 28, 29). The ECS is also a key player in virtually every aspect of the metabolic syndrome through its peripheral receptors. These include insulin sensitivity, glucose uptake, fat deposition, regulation of appetite hormones, hypertension, cardiovascular disease, atherosclerosis, systemic inflammation and permeability of the gut (13, 14, 30). The role of the ECS in the

hypothalamus, its interaction with the hormones leptin and ghrelin, and its actions on certain peripheral organs will be described more fully in the context of energy homeostasis.

CB_1 receptors are present and endocannabinoids are produced in the hypothalamus region of the brain. More specifically they are found in the hypothalamic melanocortin system, which is formed of the arcuate (ARC) and paraventricular nucleus (PVN) (31). Overall this system regulates the stress response, feeding behavior and weight gain through secondary signaling molecules such as pro-opiomelanocortin (POMC) pro-hormones. Within the ARC, endocannabinoids regulate feeding and body weight via neuropeptide Y (NPY), which when released, acts to increase feeding and produce weight gain. The endocannabinoids within the PVN along with corticotropin-releasing hormone (CRH) take part in regulation of energy homeostasis and in mediation of the stress response (29). Finally, it has been demonstrated that throughout various areas of the hypothalamus, endocannabinoid levels increase during fasting and decrease during feeding (14).

In order to regulate energy homeostasis, the ECS must receive feedback signaling from periphery systems. Leptin is one such signal that is produced by adipose tissue. It has an inhibitory effect on the production of endocannabinoids in the hypothalamus (29, 32). Thus, with the accumulation of adipose tissue, there is an increase in leptin production, which in turn acts to inhibit the orexigenic effects of the ECS in the hypothalamus and decrease feeding and weight production.

Another hormone involved in digestion is ghrelin, which also plays a similar role as the one proposed for endocannabinoids in feeding behaviors and weight gain. For

this reason their possible interaction has been of scientific interest. It has been suggested that they interact in a feed-forward manner (29). The production of ghrelin peripherally raises the levels of endocannabinoids in the hypothalamus, which in turn raise peripheral levels of ghrelin (9). The end result of this interaction is stimulation of feeding and energy storage.

Until 2003, cannabinoid receptors were thought to be located in the CNS only. In 2003, CB_1 receptors were found in white adipose tissue, which triggered extensive research into their presence in peripheral tissues where they take part in local fine-tuning of systemic energy regulation (33, 34). In adipose tissue, the ECS promotes adipogenesis through adipocyte differentiation and increased enzyme expression and activity (29). Increased activity of the ECS is positively correlated with increased fat mass (35). For example, FAAH activity, an enzyme that degrades endocannabinoids, increases with increasing BMI and waist circumference (WC) in humans (27). Furthermore, the expression of CB_1 receptors increases in obese individuals compared to non-obese individuals, and in visceral fat compared to subcutaneous fat in obese individuals (9). It was recently demonstrated in humans that insulin down-regulates the action of endocannabinoids in adipocytes (29). However, in insulin-resistant adipocytes, such as in type 2 diabetic individuals, insulin is not capable of down-regulating the endocannabinoid activity responsible for fat deposition (35).

Given the role of insulin in the regulation of endocannabinoids, it is not surprising that the ECS also acts in skeletal muscles to modulate glucose uptake (14). In animal studies, CB_1 and CB_2 receptors have been found in liver cells, where they are thought to have role in the expression of lipogenic genes (8, 14).

2.1.3. Reward circuits of the ECS

As described earlier, cannabinoid receptors are present in regions of the brain involved in reward circuits. More specifically, they can be found in the mesolimbic system where the ECS fine-tunes the reward response (28). The mesolimbic system is formed of several structures in the brain that create a pathway leading from the ventral tegmental area through the medial forebrain bundle to the striatum (28). This reward circuitry plays an important role in the motivation for and perception of "liking" aspects of behaviors such as feeding, sex and social interactions (16, 29). It controls behavior by inducing pleasurable effects, mainly through the release of dopamine, the "pleasure chemical" of the brain, within the nucleus accumbens (28). Notably, it is via this circuitry that the ECS influences palatability of food and food intake (16). The ECS is also ideally positioned to modulate the motivational and addictive effects of drugs of abuse. In animal studies, CB_1 deletion diminishes the reinforcement of most drug classes (36). In human studies, administration of a CB_1 antagonist diminishes self-administration of alcohol, opioids and nicotine (36).

2.1.4. Exogenous ligands: cannabis and synthetic antagonists

Exogenous ligands, such as cannabis and synthetic antagonists, have played an important role in developing our understanding of the ECS and will be discussed in the following section. As mentioned previously, the ECS was initially discovered through its activation by THC, the active ingredient of the *Cannabis Sativa* plant (18). Cannabis can be found in the forms of marijuana, hash or hash oils. These forms differ in their concentration of THC and their plant constituents. Marijuana contains the dried flowers and leaves of the plant and has the lowest concentration of THC of the three forms. Hash consists of the resin of the plant that is collected and

compressed. Finally, hash oil is made from extraction of the resin from the plant (37). The psychoactive ingredient that is present in the highest quantity in cannabis is THC, which is responsible for the euphoria achieved during its recreational use. The acute effects of THC include, but are not limited to, increased hunger, impaired reaction time, increased heart rate, decreased blood pressure, impaired cognitive functioning including short-term memory and executive functioning, and altered sensorial function and emotional state (18, 37, 38).

In addition to THC, the *Cannabis sativa* plant contains approximately 60 other cannabinoids. Notably cannabidiol has emerged as a compound with great therapeutic potential (13). It has low binding affinity for CB_1 and CB_2 receptors and, in contrast to THC, is non-psychotropic with anxiolytic, anti-addictive and antipsychotic properties which may serve in the treatment of neuropsychiatric disorders (18, 28, 39).

In 1994, the first selective antagonist for the CB_1 receptor, rimonabant (SR141716), was created (18). In a double-blind randomized clinical trial, rimonabant showed promising results for the treatment of the metabolic syndrome. Obese individuals who were administered 20 mg of rimonabant daily demonstrated weight loss, decrease in WC, improved lipid profiles, decrease in fatty liver and improved glucose control in diabetic individuals (15). It was also effective in treatment of nicotine dependence (20). Adverse psychiatric effects including suicide ideation resulted in its discontinuation, although many other selective antagonists, inverse agonists and neutral antagonists have since been created (15, 16).

2.1.5. Sex differences in the endocannabinoid system

Researchers have recently begun to report important sex differences in the functioning of the ECS that may be relevant to energy homeostasis and weight changes. Advances in this area have been outlined in three literature reviews, which synthesized the results of biological, pharmacological and behavioral studies in animals and humans (10-12). It has been reported that men consume greater amounts of cannabis and at a greater rate than women (12). However, women have higher activity levels of the enzymes required to metabolize THC into its bioactive form, 11-hydroxy-THC (10). Men demonstrate higher levels of circulating THC, more withdrawal symptoms and they are more sensitive to the hyperphagic and hypophagic effects of cannabis and the CB_1 antagonist respectively (12). Men may be more susceptible to the cognitive consequences of cannabis use such as decreased memory and increased risk of psychosis (11). Women with poor mental health are more at risk than other women of using cannabis as well as at increased risk of depression as a result of cannabis use, which is not the case in men (12, 40).

Female rodents are more sensitive to the down-regulating effect of leptin on endocannabinoids than male rodents (10). Important differences have also been reported in animal studies at the POMC synapses, which are involved in stress response, feeding behavior and weight gain (10). These synapses have been shown to potentiate differently in male and female animals with CB_1 activation resulting in increased excitation in females and in inhibition in males (10). Finally, the functioning of the ECS differs by sex as a result of its interaction with gonadal hormones. In females, the density of the CB_1 receptor varies with the oestrous cycle, and therefore, females are most sensitive to the effects of THC in oestrous phase (10,

12). In females, increases in POMC is dependent on estrogen (10). Finally, in males, increases induced by THC in CRH (a hormone in involved in the regulation of the stress response) are dependent on dihydrotestosterone. The three reviews all suggest that these sex differences should be taken into account in future research (10-12).

2.2.Obesity

2.2.1. Definition

Overweight and obesity are complex multifactorial conditions that are the subject of much current research. On a fundamental level, they result from an energy intake that exceeds energy expenditure. High energy intake is the result of consuming foods high in fat, sugars and salt, but low in nutritional value from vitamins, micronutrients and minerals (3). Low energy expenditure results from low levels of physical activity and high levels of sedentary behavior (41). Obesity and overweight categories are often defined by body mass index (BMI) values which are calculated by weight in kilograms divided by height in meters squared (kg/m^2). The World Health Organization (WHO) definitions for overweight and obesity are a BMI $\geq$25 and $\geq$30, respectively (3). The main health problems related to overweight are an increased risk of cardiovascular diseases, diabetes, musculoskeletal disorders and certain cancers, which together result in 2.8 million adult deaths each year (3).

Although the use of BMI as a marker for heightened health risk is widespread, controversy remains as to whether or not it is the most appropriate indicator of high risk (42). An alternate measure is waist circumference (WC), which has been proposed as a better indicator of increased cardiometabolic risk since, it indicates the inability of the body to cope with the excess energy storage (42). This

results in fat deposition in the liver, heart, skeletal muscle and visceral adipose tissue (42).

2.2.2. Trends in obesity

Although obesity rates have been rising since the beginning of the last century, it was not until 1997 that the WHO recognized obesity as a global epidemic (41). Obesity rates throughout the world have more than doubled since the 1980s (41). In 2008, there were more than 1.4 billion adults who were overweight, 200 million of whom were obese (3). In Canada in 2008, 62% of the population had a BMI greater than normal and 25% were obese based on measured height and weight (2). The prevalence of obesity increases with age until age 65, at which point it decreases (2). Among Canadian youth aged 2 to 17 years, the prevalence of obesity was 26% in 2004, an 11% increase since 1979 (43). The prevalence of obesity and overweight varies by region. In Canada, the lowest prevalence is observed in British Columbia (13%) and the highest in Newfoundland and Labrador (25%) (2). In Quebec, the self-reported prevalence of obesity is 16% and in Montreal, it is 13% (2). The cost to the health care system of obesity was estimated at 4.6 billion in Canada in 2008 (2).

2.2.3. Factors associated with overweight

Above normal BMI varies by age, sex, language and ethnicity, socio-economic status, physical activity, sedentary behavior, diet, alcohol use, mental health and smoking status (44). Further, potential determinants of obesity vary by age, sex and ethnicity (2, 45). In the following section, each of these potential determinants is discussed briefly and, where possible, their applicability to the Quebec or Canadian young adult population will be described according to sex.

As previously outlined, the prevalence of overweight and obesity increases with age up until the age of 65 years in Canada, after which it declines (2). Generally, high BMI is more prevalent in males than females (2, 44). This is true for the region of Montreal, where 59% of adult men and 40% of adult women are overweight or obese (46). Obesity and overweight also vary by ethnicity and immigration status (47). Recent immigrants have a lower prevalence of obesity compared to those who immigrated more than 10 years prior (47). Finally, within the province of Quebec, speaking a language other than French is associated with overweight and obesity in women (45).

Factors affecting energy output including physical activity and sedentary behavior are also associated with overweight. There is a lower prevalence of physical activity among overweight and obese men and women, although the prospective nature of this association remains controversial (5, 7, 43, 48). Individuals who are overweight and obese are more likely to engage in sedentary behaviors such as watching television, playing games or working on the web, playing video games, and reading (2, 5, 7).

Factors affecting energy intake directly are diet and alcohol consumption. The frequency of eating home-made meals, eating in fast food restaurants, exposure to food marketing and food insecurity all influence diet quality (2, 5). The association between alcohol use and excess weight is more pronounced in men than in women (2). Moderate alcohol intake is negatively associated with excess weight, while high alcohol intake is positively associated with excess weight in both sexes (6). Further, this association varies depending on the type of alcoholic beverage consumed; spirits

and beer are associated with increased weight, while wine is associated with decreased weight (6). Finally, overweight and obese men and women are at a decreased risk of alcohol and drug abuse (49). A possible explanation for this association is competing neuronal reward pathways within the brain (49).

Smoking influences energy intake through the effect of nicotine, which decreases appetite and increases metabolic rate (20). Smoking cessation is thought to result in increased appetite and food intake (20). Smoking is more prevalent among the overweight and obese possibly because of clustering of unhealthy behaviors or because of the known weight loss effects of smoking, particularly in women (50-52).

Finally, overweight and obesity are associated with major depression, bipolar disorder, anxiety disorder, schizophrenia and substance abuse disorders (49, 53-55). A positive bidirectional relationship is observed between above normal BMI and major depression (56, 57). Bipolar disorder and anxiety disorders are more prevalent among the overweight and obese, although the direction of the relationship is not clear (54, 56). Lastly, individuals with schizophrenia are more likely to have the metabolic syndrome (55).

2.3. Cannabis use

2.3.1. Trends in cannabis use

Globally 3-5% of individuals consume cannabis each year which, according to the WHO, makes it the leading illicit drug (17). Its prevalence has remained relatively stable worldwide over the past decade (17). The current prevalence in North America is estimated at 11% of the adult population (i.e., who report having consumed marijuana in the past year) (17). Although the prevalence has remained

relatively stable over the past decade, the concentration of THC in cannabis has increased from 4% to 13-17% percent since 1989 (38). In addition, a large number of new unregulated synthetic cannabinoids have been detected throughout the world, which are added to smoked cannabis (17). Little is known about the effects of these cannabinoids or about the extent of their use (17).

Policies and legislation concerning cannabis use are wide-ranging across the world, from its use and possession being legal but age-limited such as in the Netherlands, to possession and use being illegal, such as in most states in the United States (58). In Canada, it is illegal to possess cannabis, although an exception is made for medical use of marijuana according to the Marijuana Medical Access Regulations (59). Despite this regulation, marijuana use is widespread among Canadians. In Canada, the prevalence of cannabis use in the past year declined from 14% of the adult population in 2004 to 9% in 2011 (60). Among students in grade 7 to 12 in Ontario, one in five reported past year use of marijuana in 2011, which was double the prevalence of past-year cigarette smoking (61).

In Canada in 2011, a higher proportion of males consumed marijuana (12% compared to 7% of females) (60). The highest prevalence of use was in British Columbia and Quebec, where rates substantially exceed the national average (62). In Quebec, 51% of students in grade 11 reported past-year use and the average age at initiation was 11 years old (38). Regular cannabis use defined as once a week or more, is reported by 8% of grade 11 students (38). In Quebec, one gram of cannabis is estimated to cost $10 (38).

2.3.2. Negative health effects

There are numerous negative health effects related to cannabis use including decreased lung function, chronic obstructive disease, pneumothorax, respiratory infections, lung cancer, decreased cognitive function, mental health problems, impaired cardiovascular function as well as increased exposure to other substances of abuse such as alcohol and other illicit drugs (63-65). Aldington and Harwood (66) showed that the effect of one marijuana joint on lung cancer risk was approximately equivalent to the effect of 20 cigarettes. The effects of cannabis use on lung function have not received as much attention as its effects on mental health and cognitive functioning. There is an increased risk of developing schizophrenia particularly in early initiators and in individuals with a psychotic predisposition (28, 67, 68). Associations with decreases in memory, reflex time and IQ have also been observed, although further investigation is required (69, 70). Cannabis use is more likely among individuals with anxiety and depression, particularly in women, and cannabis use may in fact induce these conditions (28). Cannabis use also acutely impairs cognitive function, which may underpin its association with motor vehicle accidents (65, 70, 71). Other acute effects include an increased heart rate and increased blood pressure, which may lead to complications in individuals pre-disposed to developing cardiovascular disease (63, 65). Finally, as suggested by the Gateway and Reverse Gateway theories, other possible consequences of cannabis use include an increased risk of initiating other substances of abuse (20, 72). As the frequency of cannabis use increases, use of other illicit drugs and cigarettes also increase (72, 73).

2.3.3. Correlates of use

Cannabis use relates to numerous factors including sex, age, childhood socioeconomic status (SES), sedentary behavior, physical activity, diet, alcohol use, smoking status and mental health (67, 74-78). The following section elaborates on each of these using data from Quebec or Canada when available.

Cannabis use is more prevalent in males than females worldwide including in Canada and Quebec, and its use is most common in younger age groups (12, 17, 62). In Canada, the prevalence of past-year use increases until age 20 years and then decreases in each subsequent age category (62). In 2011, 22% of youth aged 15-24 years had used cannabis in the past-year, which was three times the prevalence among adults aged 25 years or older (7%) (60). A systematic review of 11 studies concluded that there was a significant association between low childhood SES and subsequent cannabis use, a finding that was consistent across studies that specifically examined the predictors of cannabis use (77, 79).

Increased sedentary behavior, and in particular computer and videogame screen time, and decreased physical activity are both associated with increased cannabis use in prospective studies (75, 78, 80). Cannabis users consume more sodium and calories than non-users and this relates primarily to increased fatty food consumption (23, 76, 81). Their alcohol intake is also higher than among non-users, which relates to increased beer and liquor consumption (23, 81). Cannabis use is more likely among individuals suffering from anxiety and depression (and, as indicated earlier, may in fact induce these states), possibly because individuals with these mental health conditions self-medicate with cannabis (67, 82, 83). Finally, cannabis users are more likely to smoke cigarettes than non-users (84). One study

conducted in the U.S. reported that 90% of cannabis users reported lifetime cigarette smoking (19).

2.4.Cigarette smoking

2.4.1. Tobacco exposure among cannabis users

As mentioned previously, cannabis and cigarette smoking tend to co-occur since they are often used within the same social environment and they share a common method of delivery - inhalation (19, 72, 84-86). Cannabis users who do not smoke cigarettes may nevertheless be exposed to tobacco directly by "chasing", which refers to smoking a cigarette immediately or shortly after smoking cannabis (86, 87). Even cannabis users who do not self-identify as cigarette smokers or smoke cigarettes may be exposed directly to tobacco through mulling or blunt smoking (86). Mulling refers to adding tobacco to cannabis prior to smoking (19, 88). It is a common practice in Europe where one study found that four of five cannabis smokers in Switzerland reported mulling. A second study conducted in the U.K. reported that 89% of cannabis users reported mulling (88). No study has yet investigated mulling in North America.

Blunt smoking is thought to be most common in North America (19, 89). A blunt consists of a cigar shell that is stuffed with cannabis (87-89). Smoking blunts exposes individuals to the tobacco and the tobacco toxins that remain in the shell. Although still under investigation, anecdotal reports suggest that individuals complement their cannabis smoking with tobacco in order to prolong the effects of cannabis, as well as increase alertness while under the euphoric effects of cannabis (90).

2.4.2. Contrasting and parallel effects of cannabis and cigarette use

Two studies that reviewed the literature examining the joint effects of cigarette and cannabis use identified cigarette smoking as an important effect modifier of the effects of cannabis on the ECS (19, 20). Nicotine and THC have both contrasting and parallel effects on addiction processes and on appetite and body weight (19, 20). In animal studies, nicotine and THC enhance each other's rewarding, physiological and behavioral effect (20). Correspondingly, regular administration of the CB_1 antagonist, rimonabant, resulted in decreased nicotine self-administration (20). Finally, qualitative studies indicate that smoking one of the two substances reinforces the other and makes cessation more challenging due to their shared route of administration and social environments (85).

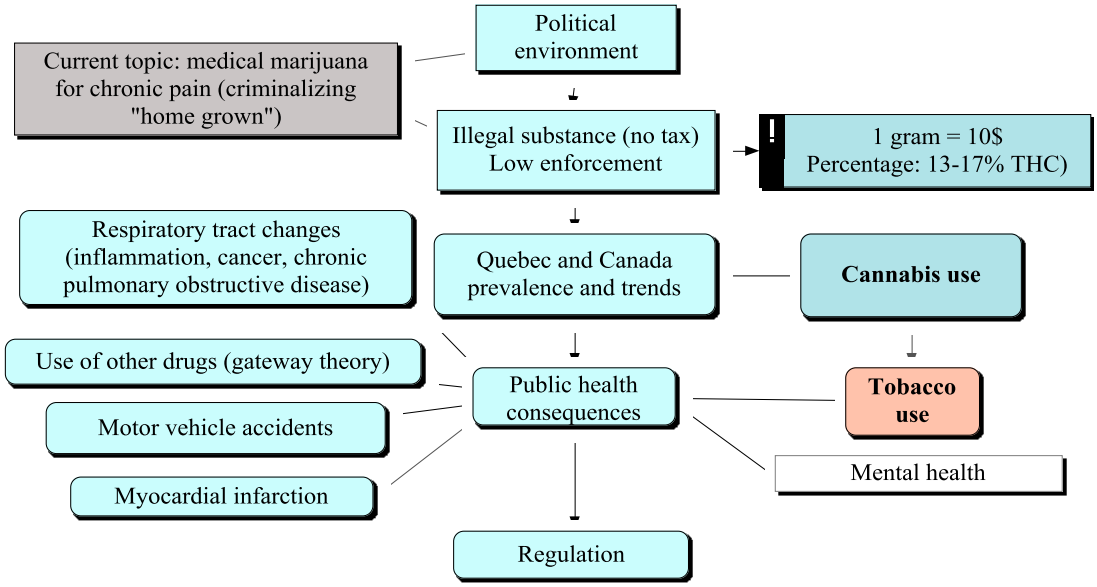
Contrasting effects are apparent with respect to appetite. Nicotine increases metabolic rate and decreases appetite, whereas cannabis stimulates appetite (20). Both act in opposing ways on leptin and NPY (20). Nicotine and cannabis exhibit both parallel and contrasting effects with respect to withdrawal symptoms. Cannabis cessation is accompanied by anger, nervousness or anxiety, craving, difficulty sleeping, decreases in appetite, weight loss and depressed mood (19, 20). Nicotine withdrawal is characterized by very similar effects on mood and craving, but rather than weight loss, it is accompanied by weight gain (19, 20).

2.5. Conceptual model

Based on the findings in this literature review, a conceptual map was developed to depict the complexity of the possible associations between cannabis use, the ECS and adiposity, as well as with the many other factors identified as linked to cannabis

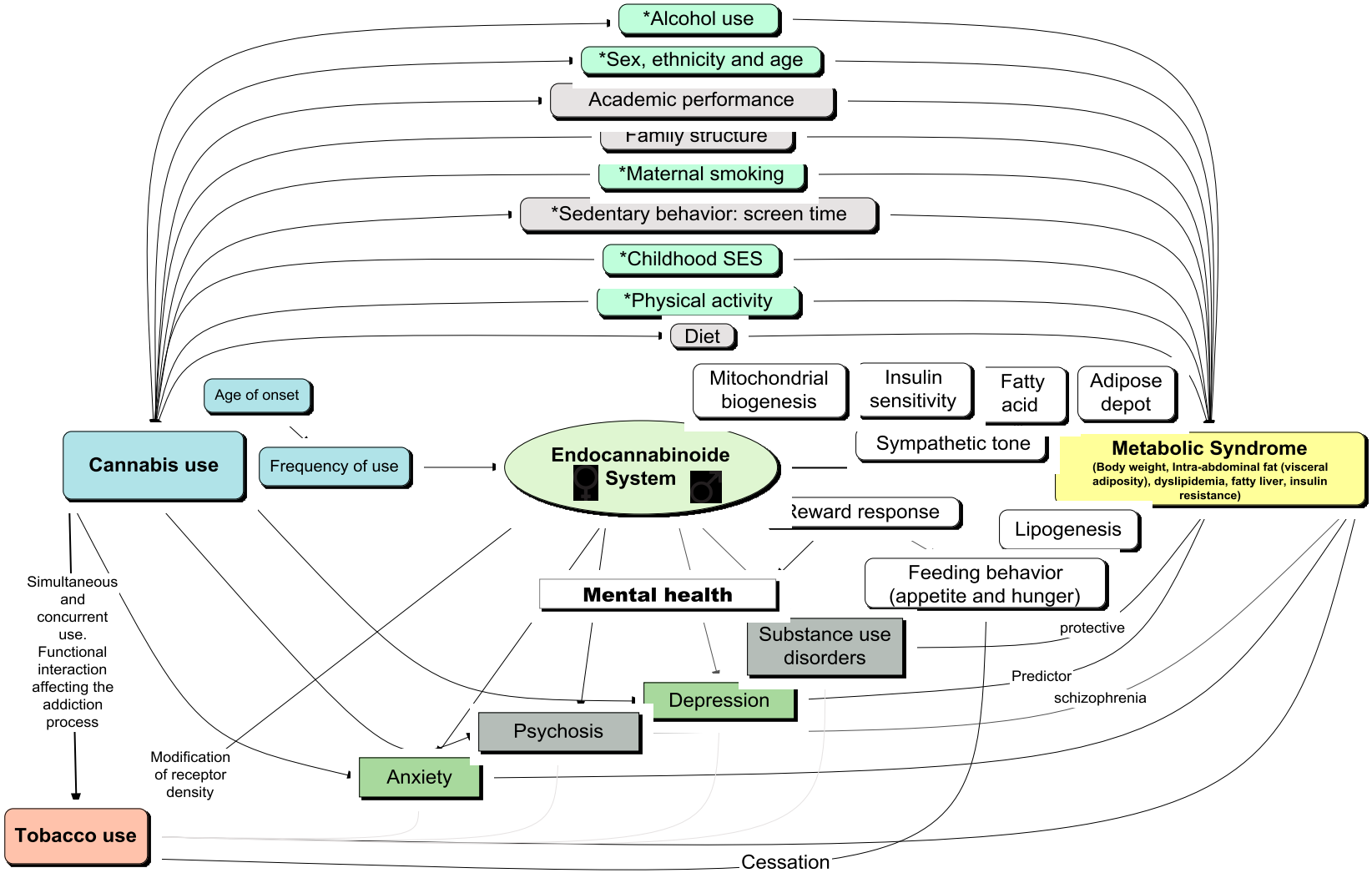
(Figure 2.1, p.21 and Figure 2.2, p.23). It places the associations of interest in public health, physiological and population-based contexts. Sex-specific differences in associations and the associations between cigarette smoking and its covariates were omitted, since their inclusion would have rendered the map too complex.

Figure 2.1: Conceptual map of the literature part A: cannabis use and society



Bidirectional arrows indicate a cross-sectional association, while unidirectional indicate an association over time. Lines without an arrowhead indicate a sub-topic

Figure 2.2: Conceptual map of the literature part B: cannabis use, the endocannabinoid system and the metabolic syndrome



Bidirectional arrows indicate a cross sectional association, while unidirectional arrows indicate an association over time.

2.6.Cannabis and adiposity: epidemiological research

2.6.1. Summary of studies to date

Only seven studies to date have examined the relationship between cannabis use and adiposity, and these studies vary substantially in methods of data collection and analysis. The methods and results of these studies are summarized in Table 2.1 (p.27). Three of five cross-sectional studies, each of which controlled for age, sex and smoking status reported a negative association between cannabis use and body mass index (BMI) (22, 23, 25). A study using data from the Third National Health and Nutrition Examination Survey (NHANES III) also adjusted for education and caloric intake in their model, although the adjusted results were not reported (23). However, unadjusted means did not demonstrate a dose-response relationship between cannabis use and BMI, although the mean BMI in current non-users was 26.6 compared to 24.7 in weekly to daily users. Another study examined data from the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) and the National Co-morbidity Survey–Replication (NCSR) separately and modeled the association between cannabis use and obesity (BMI $\geq$30 versus BMI <30) (25). Using logistic regression, they demonstrated that in each survey, the prevalence of obesity was lower in cannabis users than non-users (25% and 22% among cannabis non-users, 17% and 14% among cannabis users). A third large-scale cross-sectional study examined cannabis use and BMI in 2,566 Australian participants aged 21 year on average (22). They observed a negative dose-response trend between the risk of overweight/obese and cannabis use, after adjusting for mother's education and alcohol consumption in addition to age, sex and smoking status. However, when

sensitivity analyses were conducted separately in men and women, more frequent cannabis use was associated with greater risk of overweight and obesity in both sexes. Finally, in a sample of 297 overweight and obese women who had been referred to a weight management clinic (mean BMI = 46kg/m^2), a negative association was detected between cannabis use and BMI category (r^2 = 0.96, p = 0.017) (21). This study, however, reported few details on the methods of data collection and analysis. One of the five cross-sectional studies which included 7,825 students aged 11 to 17 years, reported that younger obese girls had a relative risk of frequent cannabis use that was three times that of normal weight girls (4). No association between cannabis consumption and weight in boys was observed.

In the longitudinal Coronary Artery Risk Development in Young Adults (CARDIA) study, there was no independent association between cannabis use and measured BMI or WC and self-report cannabis use, after controlling for gender, race, age, alcohol use, daily physical activity, physical fitness, education, income levels and cigarette smoking (81). Finally in a randomized control trial conducted in 1976 under ward condition (i.e., male participants were restricted to a hospital area), heavy cannabis users gained an average of 3.7 pounds (lbs), casual users gained 2.8 lbs and controls gained 0.2 lbs over a 21-day period of unlimited voluntary exposure (24). Given the date of the study and the lack of replication, its results should be interpreted with caution.

2.6.2. Limitations of previous studies

Cross-sectional studies that examine the association between cannabis use and adiposity cannot, by definition, model change in adiposity and therefore, the effect of

cannabis use on change in adiposity cannot be determined. These studies do suggest that cannabis users are not overweight or obese. Only two of the seven studies considered sex differences. None of these studies considered possible effect modification of the association by cigarette smoking.

Table I: Summary of studies that examine the association between cannabis use and adiposity

Study Title / Reference	Study Design	Sample and Population	Exposure measure	Outcome measure	Controls	Method of analysis	Results	Conclusion	Comments
Effects of Marihuana Use on Body Weight and Caloric Intake in Humans. Greenberg, Kuehnle (24) 1976	▪ Experimental controlled clinical trial	▪ Male volunteers ▪ 12 casual cannabis users, 15 heavy users and 10 controls	▪ 2 groups of cannabis use and one control	▪ Measured weight ▪ Caloric intake	▪ Groups were matched on socioeconomic status, level of education and intelligence	▪ Comparison of means (t-test)	▪ Heavy and casual users gained an average of 3.7 and 2.8 lbs respectively, while controls gained 0.2lbs	▪ Marijuana use is associated with increasing weight gain	▪ Ward conditions: four-bed clinical research ward of the Alcohol and Drug Abuse Research Center at the McLean Hospital ▪ 21 day period
Dietary intake and nutritional status of US adult marijuana users: results from the Third National Health and Nutrition Examination Survey Smit and Crespo (23) 2001	▪ Cross-sectional	▪ Adults aged 20-60 years who participated in NHANES III, 1988-1994 ▪ n=10,623	▪ Past-month marijuana use ▪ Three categories	▪ Body mass index ▪ Dietary intake data	▪ Age, gender, education, cigarette smoking and caloric intake	▪ Comparison of means (t-test)	▪ BMI was lower in heavy users than non-users (p=0.003) ▪ Total caloric intake was highest among heavy users	▪ BMI was slightly lower and dietary intake was different in marijuana users compared to non-users	▪ Caloric intake could be on the causal pathway and should not be controlled for ▪ Nationally representative
Body Mass Index and Marijuana Use Warren, Frost-Pineda (21) 2005	▪ Cross-sectional	▪ Women from a weight management clinic ▪ n=297	▪ Past-year marijuana use	▪ Measured BMI ▪ Four categories	▪ N/A	▪ Linear regression	▪ Negative correlation between BMI group and percent marijuana use ▪ $R^2 = 0.96$ ($p = 0.017$)	▪ As BMI increases, lower rates of marijuana use are found in females.	▪ Missing information ▪ Suggested mechanism for this association: competing effects on neurobiological reward sites

Marijuana Use, Diet, Body Mass Index, and Cardiovascular Risk Factors (from the CARDIA Study) Rodondi, Pletcher (81) 2006	▪ Longitudinal study (1985-2000)	▪ Participants in the CARDIA study ▪ n=3,617	▪ Past-month marijuana use measured 6 times over 15 years	▪ Measured BMI and waist circumference ▪ Dietary intake data	▪ Race, gender, study centre, tobacco use, amount of alcohol per day, baseline level of the dependent variables	▪ Multiple linear regression	▪ Marijuana use was associated with higher caloric intake and alcohol use ▪ Marijuana use was not significantly associated with BMI or waist circumference	▪ Marijuana use was not associated with BMI, but was associated with alcohol use, tobacco use, and high caloric intake.	▪ The relationship between BMI and marijuana use was confounded by alcohol use
Cannabis Use and Obesity and Young Adults Hayatbakhsh, O'Callaghan (22) 2010	▪ Cross-sectional	▪ Participants (age 21) of MUSP Study ▪ n=2,566	▪ Past-month marijuana use and age of onset ▪ Four categories	▪ Measured BMI ▪ Two categories: BMI<25 and BMI≥25	▪ Mother's age and level of education, age, sex, cigarette smoking, alcohol consumption, mental health, BMI at 14.	▪ Multivariate logistic regression	▪ Cannabis users were less likely to be categorized in the BMI ≥ 25 group ▪ Least prevalence observed in daily users (OR=0.2)	▪ Cannabis users were less likely to be overweight.	▪ Sensitivity analysis indicated an inverse association observed when males and females examined separately
Overweight, Obesity, Youth, and Health-Risk Behaviors. Farhat, Iannotti (4) 2010	▪ Cross-sectional	▪ Participants (age 11-17) of the Health Behaviors in School-Aged Children survey ▪ n=7,825	▪ Life-time cannabis use ▪ Three categories: abstainer, used once or twice, or other	▪ Self-report BMI ▪ Two categories: BMI<25 and BMI≥25	▪ SES, race and family composition	▪ Multinomial and logistic regression models ▪ Stratified by gender and age	▪ Obesity was associated with cannabis use among younger girls only (OR 3.4)	▪ There is a higher likelihood of substance use, among overweight and obese girls.	▪ Positive non-significant association between cannabis use and BMI. ▪ 9% of sample reported a lifetime cannabis use

Obesity and Cannabis Use: Results From Two Representative National Surveys Le Strat and Le Foll (25) 2011	▪ Cross-sectional	▪ Participants (age ≥18) of the NESARC and NCS-R ▪ n=9,879 & n= 2,283	▪ Past-year cannabis use ▪ Four categories	▪ Self-report BMI ▪ Two categories: BMI<30 and BMI≥30	▪ Sex, age, race/ethnicity, educational level, marital status, region of residence and smoking status	▪ Linear and logistic regression	▪ The prevalence of obesity was lower in cannabis users than non-users (16% vs. 22% and 17% vs. 25%)	▪ Cannabis users are less likely to be obese than non users.	▪ Low prevalence of cannabis users (4% and 7% report past-year use)

Chapter 3: Objective and hypotheses

This thesis uses data from the Nicotine Dependence in Teens (NDIT) Study (a prospective (1999-2013) cohort investigation of the natural course of nicotine dependence that collected data from 1,293 students aged 12-13 years from ten secondary schools in Montreal) to examine the possible link between cannabis use and change in adiposity in young adults. The specific objectives were to describe, in males and females separately, the association between cannabis use and change in adiposity over time, and to test if the association is modified by cigarette smoking. Based on the pharmacological and neurobiological evidence in the literature, it is hypothesized that:

i) Cannabis use is associated with greater increases in adiposity over time.

ii) The association between cannabis use and change in adiposity is modified by cigarette smoking such that cigarette smoking attenuates the association.

Chapter 4: Methods

4.1. Data source

Data for this current analysis were drawn from the Nicotine Dependence in Teens (NDIT) Study, an ongoing prospective cohort investigation of the natural course of nicotine dependence in 1,293 students aged 12-13 years at cohort inception. Participants were recruited from all grade seven classes in a convenience sample of ten secondary schools located in or near Montreal, Canada, and selected to include a mix of French and English schools, schools located in urban, suburban, and rural areas, and schools in advantaged and disadvantaged neighbourhoods. Thirteen schools were selected initially. One school was excluded because school administrators could not guarantee continued participation in the study over at least five years, and two additional schools were excluded due to low response proportions. Approximately half (55%) of eligible students participated - the low response proportion related to students' or parents' reluctance for their child to participate in the blood draw for genetic analysis, and to an ongoing labour dispute in which teachers refused to collect consent forms.

During the five years of secondary school, from grade 7 to 11 (1999 – 2005), data were collected from students in self-report questionnaires administered at school every three months during the 10-month school year, for a total of 20 survey cycles. Post-secondary school data were collected in mailed self-report questionnaires when participants were age 20 and 24 years on average, in survey cycles 21 and 22, respectively. The self-report questionnaires collected extensive data on cigarette smoking, as well as on other risk factors for chronic disease including physical

inactivity, sedentary behaviors, poor diet, alcohol use, and psychosocial characteristics. Data on illicit drug use and mental health were collected in survey cycles 21 and 22. Anthropometric characteristics (height, weight, waist circumference (WC), skinfold thickness) and blood pressure were measured in survey cycles 1, 12, 19 and 22, and blood and saliva samples were collected in grade 9 and in survey cycles 21 and 22 to enable investigation of genetic risk factors. Finally, parental data were collected in 2007.

The NDIT Study is funded by the Canadian Cancer Society. At baseline, participants provided assent and a parent or guardian provided written informed consent. Participants themselves provided informed consent in the post-secondary school data collections. NDIT received ethics approval from the Montreal Department of Public Health Ethics Review Committee, the McGill University Faculty of Medicine Institutional Review Board and the Ethics Review Committee at the CRCHUM.

4.2. Study Design

The objectives of this thesis were addressed in a prospective cohort study design stratified by sex, which examined the associations between past year cannabis use (measured in survey cycle 21 when participants were age 20.4 years on average) and change in BMI and WC over seven years during young adulthood (i.e., from survey cycle 19 to 22). Although BMI and WC are both indicators of adiposity, contrasting results across these two outcomes could indicate a difference in lipodistophy (i.e., the functioning of different types of adipose tissue). This speculation is supported by the physiological importance of the ECS in adipose tissue regulation. Covariates

included physical activity, sedentary behavior and alcohol use (in males only) which were measured in survey cycles 17-20, when participants were in grade 11 and age 17 years on average. BMI and WC as measured in survey cycle 19 were also included as covariates.

4.3. Analytic sample

Eligibility criteria for inclusion in the current analysis were that the:

(i) participant completed the self-report questionnaire in survey cycle 21, which collected data on lifetime as well as current frequency of cannabis use and self-reported height and weight. A total of 880 of 1,293 NDIT participants completed survey cycle 21, of which 404 were male and 476 were female.

(ii) participant had values for measured height and weight in survey cycle 22. Of 880 participants who completed self-report questionnaires in survey cycle 21, 160 were excluded based on this criterion. Therefore the analytic samples were reduced to 327 males and 393 females.

(iii) participant had values for measured height and weight in survey cycle 19 or self-reported height and weight in survey cycle 21. No participants were excluded based on this criterion.

(iv) participant had values for measured WC in survey cycle 19. For analyses conducted using change in WC as the outcome variable, 180 participants were excluded based on this criterion, so that the analytic subset was reduced to 256 males and 284 females.

(v) participant had complete data on the exposure, outcome and covariates. A further 130 participants were excluded due to missing data, erroneous measures, or outliers. Therefore the final analytic samples for the analysis conducted using BMI were 271 males and 319 females. Analyses conducted using change in WC as the outcome variable included 250 males and 283 females.

4.4. Study variables

The specific questionnaire items that are relevant to this thesis are described in Appendix 1.

4.4.1. Cannabis use

Cannabis use was measured in survey cycle 21 by: "In the past 12 months how often did you… use marijuana, cannabis, hashish". Response choices included: "never", "less than once per month", "1-3 times per month", "1-6 times per week", or "every day, which were re-coded for analysis to represent weekly frequency of use (i.e., 0, 0.1, 0.4 3, and 7 times per week).

4.4.2. Cigarette smoking

Lifetime cigarette use was measured in all survey cycles by: "Have you ever in your life smoked a cigarette, even just a puff (drag, hit, haul)?" Participants who responded no were coded as smoking 0 cigarettes per day. Participants who responded "yes" completed a 3-month recall of cigarette use which included the three questions presented in Table II (p.39). Questions 1 and 2 were asked for each of the three months preceding questionnaire administration.

For analysis, mean number of cigarettes smoked per day in each of the past three months was computed as the number of days smoked per month multiplied by

the number of cigarettes usually smoked each day on the days that the participant smoked. The mean number of cigarettes smoked per day was averaged across the three months. Test-retest reliability of the past three-month recall is very good (91). A total of 232 participants were missing data on past three-month cigarette smoking; cigarette smoking for these participants was imputed based on their response to question 3 in Table II (p.39).

Table II: Questionnaire items, response choices and coding used to represent daily cigarette smoking

Questionnaire item	**Response choices**	**Coding used**
1. "How many days did you smoke cigarettes, even just a puff during [the last month, month before last, and the before last month]?"	None	0 days
	1 day	1 day
	2-3 days	2.5 days
	4-5 days	4.5 days
	6-10 days	8 days
	11-15 days	13 days
	16-20 days	18 days
	21-30 days	25.5 days
	Every day	30 days
	Don't know	Missing
2. "On the days that you smoked during [the last month, month before last, and the before last month], how many cigarettes did you usually smoke each day?"	< 1 cigarette	0.5 cigarettes
	2-3 cigarettes	2.5 cigarettes
	4-5 cigarettes	4.5 cigarettes
	6-10 cigarettes	8 cigarettes
	11-15 cigarettes	13 cigarettes
	16-20 cigarettes	18 cigarettes
	21-25 cigarettes	23 cigarettes
	>25 cigarettes	26 cigarettes
3. "Check the box that describes you best…".	"I have smoked cigarettes, but not at all in the past 12 months"	0 cigarettes/day
	"I smoked cigarettes once or a couple of times in the past 12 months"	0.01 cigarettes/day
	"I smoke cigarettes once or a couple of times each month"	0.05 cigarettes/day
	"I smoke cigarettes once or a couple of times each week"	0.2 cigarettes/day
	"I smoke cigarettes every day"	1 cigarettes/day

4.4.3. Anthropometric measures

Height, weight and WC were measured in survey cycles 19 and 22 by trained technicians according to standardized protocols (92). Two measures to the nearest

0.1cm for height and WC, and 0.2kg, for weight, were recorded. If they differed by more than 0.5cm and 0.2kg respectively, a third measure was taken, and the average of the two closest measures was used in the analysis. Inter-rater reliabilities (split-half coefficients) computed using repeat measures for one in 10 participants were 0.99, 0.99, and 0.98 for height, weight and WC, respectively (93). Body mass index (BMI) was computed by dividing weight (in kg) by height (m^2). Change in BMI and WC over time was computed for each participant by subtracting their BMI or WC value from survey cycle 19 from the BMI or WC values in survey cycle 22.

Because 189 participants were missing anthropometric data in survey cycle 19, we modeled BMI for survey cycle 19 using data on self-report height and weight (i.e., BMI) from survey cycle 21 according to the following linear regression:

$$BMI_{sc19} = 2.378 + 0.886 * BMI_{sc21}$$

Values predicted using this equation were strongly correlated with measured BMI in survey cycle 19 ($r= 0.83$; $p<0.001$) among participants with measured height and weight in survey cycle 19. Because there were no data on self-report WC in survey cycle 21, imputation of WC values for survey cycle 19 was not possible.

4.4.4. Covariates

Socio-demographic characteristics

Data on sex, which were collected in multiple surveys, were verified for consistency across survey cycles. Data on mother's education were collected in the parental questionnaire and coded for analysis as mother university-educated (yes, no).

Physical activity

Physical activity was assessed in a 7-day recall in which participants recorded on which day(s) during the previous week they had participated in any of 29 common physical activities for ≥ 5 minutes (94). Activities were categorized as light, moderate, or vigorous, and the number of times the participants reported moderate or vigorous activities per week summed and averaged over survey cycles 17-20 (95). The moderate/vigorous physical activity score ranged from 0 to 55 times per week.

Sedentary behavior

Computer time was measured by asking participants to indicate the number of hours spent per day using the internet, working on the computer or playing videogames. In addition, participants were asked to indicate, the number of hours spent watching television on weekdays and on weekends. Number of hours per day on weekdays was multiplied by five and added to number of hours per day on weekends multiplied by two. This sum was then divided by seven to provide an average number of hours of television per day. Values >18 hours per day was deemed not possible and coded as missing.

Alcohol use

Alcohol use was measured in survey cycle 17-20 by asking participants how often they drank alcohol in the past month. Response choices included never, a bit to try, once or a couple of times a month, once or a couple of times a week, daily, which were re-coded as 0, 0.5, 2, 8, and 30 times per month. Responses across survey cycles were averaged to represent mean monthly alcohol consumption.

Mental health

Mental health was assessed using three indicators. In survey cycles 17 to 20, a score was computed for each participant based on the 6-item Mellinger depression symptoms scale (96, 97). Participants were asked how often in the past three months they had felt: too tired to do things; felt hopeless about the future; felt nervous or tense; worried too much about things; had trouble going to sleep or staying asleep; felt unhappy, sad or depressed. Response choices included never, rarely, sometimes, and often scored 1, 2, 3, and 4, respectively. An average of the scores was computed, resulting in values that ranged from 1 to 4. Participants who responded to fewer than four of the six items were coded as missing. Scores across survey cycles 17-20 were averaged. Participants with higher scores had more depressive symptoms. In addition to the depression score, in survey cycle 21, participants were asked if a health professional had ever diagnosed them (yes, no) with a mood disorder (i.e., depression, bipolar disorder) or an anxiety disorder (i.e., phobia, fear of social situations, obsessive-compulsive disorder, panic disorder, generalized anxiety disorder).

4.5. Data analysis

4.5.1. Descriptive analysis

The frequency distributions of the outcome variables were examined to ensure they was normally distributed and to identify outliers. Their distributions were also examined according to each categorical variable. Frequency distribution of continuous variable and their mean, range and variance were used to detect

implausible values and possible outliers. Implausible values were re-coded as missing.

The number of participants with missing data for each variable is described in Table III (p.43). The final BMI regression models, which included only participants with complete data, included of 271 males and 319 females. The final WC regression models included 250 males and 283 females.

Table III: Number of participants with missing data according to study variable

Variable	**Missing from analytic sample for BMI analyses n**		**Missing from analytic sample for WC analyses n**	
	Male	***Female***	***Male***	***Female***
Maternal education	27	34	9	7
Sedentary behavior	51	72	0	0
Alcohol use	52	72	0	0
Physical activity	53	73	2	1
Depression symptoms	51	72	0	0
Diagnosed anxiety or mood disorder	2	0	2	0

The sample was stratified by sex and described according to socio-demographic and lifestyle characteristics. Cannabis use, change in BMI and change in WC were examined according to socio-demographic and lifestyle characteristics in each group. An ANOVA was used to test for differences between means for the continuous variables grouped by each categorical variable.

4.5.2. Univariate analyses

Mean change in BMI and WC over seven years (from survey cycle 19 to 22) for each sex was plotted by frequency of cannabis use. In order to accommodate the U-shaped association indicated in the figures, a quadratic term was created by computing the square of the cannabis variable. The crude association was further examined in polynomial regression models of change in BMI or WC predicted by

cannabis use and cannabis use squared. This method was selected to take advantage of the continuous nature of the outcome variables, and to accommodate the U-shaped association observed in the univariate analysis.

4.5.3. Multivariate analyses

Potential confounders of the association between cannabis use and change in adiposity were selected based on a correlation matrix as those variables that were correlated at r ≥0.2 with cannabis use. Among male participants, alcohol use was the only variable correlated with cannabis use at this level. In female participants, none of the covariates examined were correlated with cannabis use at this level. Although not correlated at r ≥0.2, physical activity and sedentary behavior were included in the models, since these variables are widely believed to be associated with adiposity. Finally, baseline BMI and baseline WC were included in the models to account for biological and/or societal predisposition for a high BMI or WC.

The association between cannabis use and change in each of the two adiposity indicators (BMI and WC) was examined multivariately in polynomial regression models for each sex separately. The adjustment for alcohol use was only included in the model fitted to the male participants' data, and is not presented in the equations below. The first model for female participants (which does not include an interaction term between cannabis use and cigarette smoking) is represented by the following two equations (one equation for each outcome variable):

i. $\Delta BMI_i =$

$\beta_1 * cannabis_i + \beta_{11} * cannabis^2{}_i + \beta_2 * cigarette_i + \beta_3 * phsyical\ activity_i + \beta_4 * sedentary\ beh._i + \beta_5 * BMI_{Baseline_i} + \varepsilon_i$

ii. $\Delta WC_i =$

$\beta_1 * cannabis_i + \beta_{11} * cannabis^2{}_i + \beta_2 * cigarette_i + \beta_3 * phsyical\ activity_i + \beta_4 *$

$sedentary\ beh._i + \beta_5 * WC_{Baseline_i} + \varepsilon_i$

The second model fitted to female participants' data included interaction terms to test if the association between cannabis use and change in adiposity indicators was modified by cigarette smoking:

i. $\Delta BMI_i = \beta_1 * cannabis_i + \beta_{11} * cannabis^2{}_i + \beta_2 * cigarette_i + \beta_{12} * (cigarette_i *$

$cannabis_i) + \beta_{112} * (cigarette_i * cannabis^2{}_i) + \beta_3 * alcohol_i + \beta_4 *$

$phsyical\ activity_i + \beta_5 * sedentary\ beh._i + \beta_6 * BMI_{Baseline_i} + \varepsilon_i$

ii. $\Delta WC_i = \beta_1 * cannabis_i + \beta_{11} * cannabis^2{}_i + \beta_2 * cigarette_i + \beta_{12} * (cigarette_i *$

$cannabis_i) + \beta_{112} * (cigarette_i * cannabis^2{}_i) + \beta_3 * alcohol_i + \beta_4 *$

$phsyical\ activity_i + \beta_5 * sedentary\ beh._i + \beta_6 * WC_{Baseline_i} + \varepsilon_i$

The statistical significance of each beta coefficient was determined using the Wald test. To test the combined significance of the pair of interaction terms for both the BMI and WC models, a full model, which included the interaction terms "cannabis use and cigarette smoking", and "cannabis use squared and cigarettes smoking", was compared to a reduced model, which excluded the two interaction terms using a likelihood ratio test. This test follows a χ^2 distribution with 2 degrees of freedom (the difference in the degrees of freedom of the full and reduced models).

After fitting the initial models, possible multicollinearity related to inclusion of collinear terms (i.e., cannabis use, cannabis use squared, their interaction terms) was investigated by examining the variance inflation factors (VIFs). Multicollinearity was an issue as evidenced by VIFs that exceeded 10 for cannabis use, cannabis use squared, cigarette smoking and the interaction terms. To rectify this situation,

cannabis use and cigarette smoking were each centered around a constant (i.e., the mean corresponding to a value of 2.257 times per week for cannabis use, and 4.940 cigarettes per day for cigarette smoking) in both sexes. These values were subtracted from each cannabis use and cigarette smoking value. The VIFs for the models that incorporated centered values for cannabis use and cigarette smoking were reduced to values deemed tolerable.

The residuals of each model were examined to ensure that model assumptions were met, to identify outlying residuals and to assess the stability of the model. This was completed by viewing the distribution of the standardized residuals to ensure that they were normally distributed. A normal probability plot of the standardized residuals was also examined to assess the distribution of the residuals. Scatter plots were used to ensure that the error was equally distributed across independent variables, and that no patterns were observed. Outlying values were identified by examining the magnitude of the standardized residuals. Potentially outlying values were re-examined and their influence on the model assessed. Influential values were examined using Cook's Distance and Leverage values. The influence of large values on the beta coefficients was analyzed. These values served as an indication of the stability of the model.

Because interpretation of a polynomial regression with an interaction term and centered variables is challenging, we plotted the association between cannabis use and change in BMI and WC in each final model for two hypothetical individuals – one who smoked half a cigarette per day, and one who smoked 15 cigarettes per day. Finally, a three dimensional graphing tool was used to identify the approximate

stationary points of the curve in models containing an interaction term and rearrangement of the model equations used to determine their values. All statistical analyses were conducted using the IBM SPSS Statistics package version 20 (International Business Machines Corp., Armonk, NY).

Chapter 5: Manuscript

Preface

This chapter presents the results of this study in manuscript format. My specific contributions to this work were the development of the initial idea for this study, the completion of the literature review, the statistical analysis, interpretation of the findings and the writing of the thesis and manuscript. The support, guidance and critiques of my supervisors: Dr. J. O'Loughlin, Dr. D. Jutras-Aswad and Dr. I. Karp were essential in each step in this study and to my development as a researcher. The figures and tables that could not be incorporated into the manuscript due to space limitations are included in Appendix 2 and 3.

Manuscript

Title of manuscript:

Does cigarette smoking modify the association between cannabis use and change in adiposity in young men and women?

Authors: Emily Dubé, Jennifer O'Loughlin, Ph.D., Igor Karp, M.D., Ph.D.
& Didier Jutras-Aswad, M.D., M.Sc., FRCPC

To be submitted to: Addiction Biology

Abstract

Aim: To test the hypothesis that the association between cannabis use and change in adiposity is modified by cigarette smoking.

Design: Cohort study

Setting: Montreal, Canada

Participants: 271 males and 319 females aged 24 years on average participating in the Nicotine Dependence In Teens (NDIT) Study, a 13-year prospective cohort investigation of the natural course of nicotine dependence.

Measurements: Cannabis use was measured as past-year cannabis use when participants were 20 years of age on average. Cigarette smoking was also measured at age 20 years as the number of cigarettes per day over a three-month recall period. Outcome measures included change in body mass index (BMI) and in waist circumference (WC) from age 17 to 24 years.

Data analysis: Possible effect modification of the associations between cannabis use and change in BMI and change in WC by cigarette smoking was tested in polynomial linear regression models adjusting for covariates in males and females separately.

Findings: In males, the interaction between cannabis use and cigarette smoking was statistically significant in both the model for change in BMI ($p=0.004$) and the model for change in WC ($p=0.036$). In females, the interaction between cannabis use and cigarette smoking was not statistically significant in either model. Cannabis use was associated with change in adiposity in a U-shaped association in females and in male non-smokers, and in an inverted U-shaped association in male smokers.

Conclusion: Smoking cigarettes appears to attenuate the association between cannabis use and change in adiposity in young men, but not in young women.

Introduction

The ongoing obesity epidemic is of considerable concern worldwide. In Canada, 62% of the population is overweight or obese, and the healthcare burden associated with obesity is estimated at $4.3 billion annually in direct and indirect costs (1, 2). Extensive research has identified numerous risk factors for excess body weight including poor diet and low levels of physical activity, which have both been important targets for lifestyle-oriented public health programs and policy. A target of pharmaceutical weight loss interventions has been the endocannabinoid system (ECS), since its over-activation is associated with overweight and obesity (8, 9, 31).

The ECS is implicated in the maintenance of energy homeostasis through its signalling molecule and receptors, which include the cannabinoid-1 (CB_1) and cannabinoid-2 (CB_2) receptors (14). ECS receptors in the central nervous system are involved in motivation to eat, perceived palatability of food, suppression of aversive memory, creation of a stress response and emotional regulation (9, 28, 29). Through its peripheral receptors, the ECS is implicated in virtually every aspect of the metabolic syndrome and its associated symptoms including insulin sensitivity, glucose uptake, fat deposition, appetite hormone regulation, hypertension, cardiovascular disease, atherosclerosis, systemic inflammation, and permeability of the gut (13, 14, 30).

ECS actions differ according to sex at a cellular level and at the endocrine level due to an interaction with the sex hormones (10-12). Its homeostatic effects as a

result of stimulation by exogenous cannabinoids are more extreme in men, while its effects on mood, particularly anxiety and depression, are more extreme in women (10).

Cannabis is the most widely used illicit drug in the world, with an estimated 125 to 203 million users in 2009 (17). Its use relates to age, childhood socioeconomic status (SES), sedentary behavior, physical activity, diet, alcohol use, smoking status and mental health, and its use is more common in men than women (67, 74-78). The non-synthetic cannabinoid that first led to the identification of the CB_1 receptor, was delta-9-tetrahydrocannabinol (THC), the active component of the *cannabis sativa* plant, which acts agonistically on the receptor (18).

The immediate effects of THC on appetite are well-known and synthetic derivatives of THC are used for their orexigenic effects in patients suffering from anorexia nervosa and acquired immune deficiency syndrome (14, 16). However, there are numerous negative health consequences that can result from smoking cannabis including impaired lung function (i.e., chronic obstructive disease, pneumothorax, respiratory infections, and lung cancer), cognitive function, mental health, cardiovascular function as well as increased exposure to other substances of abuse such as alcohol and illicit drugs (63-65).

When used recreationally, cannabis is smoked and often co-used or used simultaneously with tobacco (19). Among cannabis users in the U.S., 90% reported having been a cigarette smoker (19). Cannabis users who do not self-identify as cigarette smokers or smoke cigarettes may also be exposed directly to tobacco through mulling (86), which refers to adding tobacco to cannabis prior to smoking,

and is a common practice in Europe (19, 88). No study has yet investigated mulling in North America.

Human and animal studies examining the joint effects of cigarette and cannabis use have identified nicotine as an important modifier of the action of THC on the ECS (20). Nicotine and THC have both contrasting and parallel effects on addiction processes and on appetite and body weight (19, 20). Nicotine increases metabolic rate and decreases appetite, while cannabis stimulates appetite (20). Both act in opposing ways on leptin and neuropeptide Y (NPY), two hormones involved in digestion (20). These differences become evident in cessation: cannabis cessation is accompanied by a decrease in appetite and weight loss, while nicotine withdrawal is accompanied by increased weight and cravings (19, 20).

To date, studies that investigate the association between cannabis use and weight are inconclusive (4, 21-25). Most extant studies are cross-sectional and none have specifically tested for modification of the effect of cannabis use on change in adiposity by cigarette smoking. Also, few studies have investigated possible differences in these associations according to sex. This current study describes the association between cannabis use and change in adiposity in males and females separately, and tests if this association is modified by cigarette smoking. We hypothesize, given that THC stimulates the ECS and over-activation of the ECS is observed in overweight and obese individuals, that cannabis use leads to weight gain, but that this effect is modified by cigarette smoking.

Methods

Data were drawn from the Nicotine Dependence in Teens (NDIT) Study, an ongoing prospective cohort investigation of the natural course of nicotine dependence in 1,293 students aged 12-13 years at cohort inception. Participants were recruited from all grade seven classes in a convenience sample of ten secondary schools located in or near Montreal, Canada, which were selected to include a mix of French and English schools, schools located in urban, suburban, and rural areas, and schools in advantaged and disadvantaged neighbourhoods. Thirteen schools were selected initially. One school was excluded because school administrators could not guarantee continued participation in the study over at least five years, and two additional schools were excluded due to low response proportions. Approximately half (55%) of eligible students participated - the low response proportion related to students' or parents' reluctance for their child to participate in the blood draw for genetic analysis, and to an ongoing labour dispute in which teachers refused to collect consent forms.

During the five years of secondary school, from grade 7 to 11 (1999 – 2005), data were collected from students in self-report questionnaires administered at school every three months during the 10-month school year, for a total of 20 survey cycles. Post-secondary school data were collected in mailed self-report questionnaires when participants were age 20 and 24 years on average, in survey cycles 21 and 22, respectively. The self-report questionnaires collected data on cigarette smoking, as well as on physical activity, sedentary behaviors, diet, alcohol use, and psychosocial characteristics. Data on illicit drug use were collected in survey cycles 21 and 22. Anthropometric characteristics (height, weight, waist circumference (WC)) were

measured in survey cycles 1, 12, 19 and 22. Finally parental data, including maternal education, were collected in 2007.

Study variables

Cannabis use frequency was measured by: “In the past 12 months how often did you… use marijuana, cannabis, hashish”. Response choices included: “never”, “less than once per month”, “1-3 times per month”, “1-6 times per week”, or “every day”, which were re-coded for analysis to represent weekly frequency of use (i.e., 0, 0.1, 0.4, 3, and 7 times per week, respectively).

Lifetime cigarette use was measured by: “Have you ever in your life smoked a cigarette, even just a puff (drag, hit, haul)?” Participants who responded no were coded as smoking 0 cigarettes per day. Participants who responded “yes” completed a 3-month recall of cigarette use which included two items: (i) “On how many days did you smoke cigarettes, even just a puff during [the last month, month before last, and two months before last]?” for each of the past three months; and (ii) “On the days that you smoked during [the last month, month before last, and the before last month], how many cigarettes did you usually smoke each day?” Mean number of cigarettes smoked per day in each of the past three months was computed as the number of days smoked per month multiplied by the number of cigarettes usually smoked each day on the days that the participant smoked divided by 30. The mean number of cigarettes smoked per day was averaged across the three months. Test-retest reliability of the past three-month recall is very good (91).

Height, weight and WC were measured by trained technicians according to standardized protocols (92). Two measures to the nearest 0.1cm for height and WC,

and 0.2kg, for weight, were recorded. If they differed by more than 0.5cm or 0.2kg respectively, a third measure was taken, and the average of the two closest measures was used in the analysis. Inter-rater reliabilities (split-half coefficients) computed using repeat measures for one in 10 participants were 0.99, 0.99, and 0.98 for height, weight and WC, respectively (93). Body mass index (BMI) was computed by dividing weight (kg) by height (m^2). Change in BMI and WC between age 17 and 24 years were computed by subtracting the value of BMI and WC in survey cycle 19 from their values in survey cycle 22.

A total of 189 participants were missing anthropometric data in survey cycle 19. In order to impute these missing data, a regression model was fitted using data for participants who had both anthropometric measurements in survey cycle 19 and self-report data in survey cycle 21. The regression model was used to impute BMI in survey cycle 19 as a function of self-report BMI in survey cycle 21. Values thus predicted were strongly correlated with actual measured BMI values in survey cycle 19 ($r=0.83$; $p<0.001$).

Data on mother's education were collected in the parental questionnaire and coded for analysis as mother university-educated (yes, no).

Physical activity was assessed in a 7-day recall in which participants recorded on which day(s) during the previous week they had participated in any of 29 common physical activities for ≥5 minutes (94). Activities were categorized as light, moderate, or vigorous, and the number of times the participants reported moderate or vigorous activities per week was summed and averaged over survey cycles 17-20 (95). The moderate/vigorous physical activity score ranged from 0 to 55 times per week.

Sedentary behavior was measured by first asking participants to indicate the number of hours spent per day using the internet, working on the computer or playing videogames. In addition, participants were asked to indicate, the number of hours spent watching television on weekdays and on weekends. Number of hours per day on weekdays was multiplied by five and added to number of hours per day on weekends multiplied by two. This sum was then divided by seven to provide an average number of hours of television per day. Values >18 hours per day was deemed not possible and coded as missing.

Alcohol use was measured in survey cycle 17-20 by asking participants how often they drank alcohol in the past month. Response choices included never, a bit to try, once or a couple of times a month, once or a couple of times a week, daily, which were re-coded as 0, 0.5, 2, 8, and 30 times per month. Responses across survey cycles were averaged to represent mean monthly alcohol consumption.

Mental health was assessed using three indicators. In survey cycles 17 to 20, a score was computed for each participant based on the 6-item Mellinger depression symptoms scale (96, 97). Participants were asked how often in the past three months they had felt: too tired to do things; felt hopeless about the future; felt nervous or tense; worried too much about things; had trouble going to sleep or staying asleep; felt unhappy, sad or depressed. Response choices included never, rarely, sometimes, and often scored 1, 2, 3, and 4, respectively. An average of the scores was computed, resulting in values that ranged from 1 to 4. Scores across survey cycles 17-20 were averaged. In addition to the depression score, in survey cycle 21, participants were asked if a health professional had ever diagnosed them with a mood disorder (i.e.,

depression, bipolar disorder) (yes, no) or an anxiety disorder (i.e., phobia, fear of social situations, obsessive-compulsive disorder, panic disorder, generalized anxiety disorder) (yes, no).

Statistical Analysis

The frequency distributions of the outcome variables were examined to ensure that they were normally distributed and to identify outliers. Their distributions were also examined according to each categorical variable. Frequency distribution of continuous variable and their mean, range and variance were used to detect implausible values and possible outliers. The sample was stratified by sex and described according to socio-demographic and lifestyle characteristics. Cannabis use, change in BMI, and change in WC were examined according to socio-demographic and lifestyle characteristics in each group. Mean change in BMI and WC for each sex was plotted by frequency of cannabis use. In order to accommodate the U-shaped association between cannabis use and change in adiposity indicated by the figures (Appendix 1: Figure A.1 to Figure A.4), a quadratic term was created for cannabis use. The crude association was further examined in polynomial linear regression models of change in BMI or WC regressed on cannabis use and cannabis use squared. Accordingly, the models included interaction terms for "cannabis use and cigarette smoking", and "cannabis use squared and cigarette smoking".

Potential confounders of the association between cannabis use and change in BMI or change in WC included sedentary behavior, physical activity, alcohol use, anxiety and depression diagnosis, depression symptoms and maternal education. These potential confounders were selected based on a correlation matrix as those

variables that were correlated at r ≥0.2 with cannabis use. Among male participants, alcohol use was the only variable correlated with cannabis use at this level. In female participants, none of the covariates examined were correlated with cannabis use at this level. However, although not correlated at r ≥0.2, physical activity and sedentary behavior were included in the models for both males and females since these variables are widely believed to be associated with adiposity. BMI and WC in survey cycle 19 were also included as covariates in the model.

The statistical significance of all beta coefficients in the model was determined using the Wald test. To test the statistical significance of the interaction terms (i.e., "cannabis use and cigarette smoking", and "cannabis use squared and cigarette smoking"), a full model (including both interaction terms) was compared to a reduced model (excluding the two interaction terms) using a likelihood ratio test.

Multicollinearity between the cannabis use beta coefficients was expected as a result of a high level of correlation between cannabis, cannabis use squared, cigarette smoking, "cannabis use and cigarette smoking", and "cannabis use squared and cigarettes smoking". The variance inflation factors (VIFs) of these interaction terms exceeded ten, indicating a high level of multicollinearity. To reduce the potential for multicollinearity, values for cannabis use and cigarette smoking were centered around the mean value for cannabis use and the mean value for number of cigarettes smoked per day respectively. Sensitivity analyses were undertaken to ensure that the choice of the constant was appropriate by ensuring that centering by different constants did not have an impact on the value of the beta coefficient. The variance inflation factors (VIFs) of the resulting models were acceptable (VIF<6).

The residuals of each model were examined to ensure that model assumptions were met, to identify outlying residuals and to assess the stability of the model. Potentially outlying values were re-examined and their influence on the model assessed. Influential values were examined using Cook's Distance and Leverage values. The influence of large values on the coefficients was analyzed.

Because interpretation of a polynomial regression with an interaction term and centered variables is challenging, we plotted the association between cannabis use and change in BMI and WC in each final model for two hypothetical individuals – one who smoked half a cigarette per day, and one who smoked 15 cigarettes per day. Finally, a three dimensional graphing tool was used to identify the approximate stationary points of the curve in models containing an interaction term and rearrangement of the model equations used to determine its value.

Results

Most male participants (93%) were born in Canada; 72% spoke a language other than French (primarily English); and 53% had university-educated mothers (Table IV, p.65). Seventy-nine percent had a BMI <25, 60% were non-smokers and most drank alcohol occasionally to weekly (38%). Similarly, most female participants (94%) were born in Canada; 69% spoke a language other than French (primarily English); and 45% had university-educated mothers. Most female participants (84%) had BMI < 25, 54% were non-smokers and 53% drank alcohol occasionally to weekly.

Table IV (p.27) reports cannabis use frequency according to selected socio-demographic and lifestyle-related characteristics in males and females. The results

suggest that in males, a higher proportion of participants who did not speak French (i.e. who spoke English primarily) used cannabis; while, in females, a higher proportion of participants who spoke French used cannabis. In both males and females, the frequency of cannabis use increased with increased number of cigarettes smoked per day and decreased physical activity. In addition, in males, the frequency of cannabis use increased as the frequency of alcohol use increased. Finally, in both males and female participants, regular cannabis users (defined as weekly or more) were all born in Canada. The unadjusted mean change in BMI differed significantly across cannabis use in both male and female participants (Table V, p.67). Change in WC was not statistically significantly different across cannabis use in either sex.

Table IV: Cannabis use by selected socio-demographic and lifestyle-related characteristics in males and females. NDIT Study, 2005-2012										
	Male					***Female***				
	Cannabis use (times per week)									
	0	0.1	0.4	3	7	0	0.1	0.4	3	7
	n=152 (56%)	*n=46* (17%)	*n=22* (8%)	*n=25* (9%)	*n=26* (10%)	*n=181* (57%)	*n=65* (20%)	*n=23* (7%)	*n=31* (10%)	*n=19* (6%)
	%	**%**	**%**	**%**	**%**	**%**	**%**	**%**	**%**	**%**
French-speaking	32	26	26	20	15	33	20	44	23	42
Born in Canada	92	89	96	100	100	91	99	96	100	100
Mother university-educated	48	67	48	64	46	42	59	39	38	47
BMI (kg/m^2)										
<25	78	85	78	80	73	82	89	87	87	79
≥25 >30	16	13	13	16	23	13	8	4	10	11
≥30	6	2	9	4	4	5	3	9	3	11
WC (cm) ≤ median	49	47	52	60	46	51	54	55	42	40
No. cigarettes smoked/day										
Non users	78	52	35	24	19	68	52	35	23	11
1st tertile	11	30	17	12	8	14	21	22	20	16
2nd tertile	4	11	39	32	35	10	17	22	33	26
3rd tertile	7	7	9	32	39	9	11	12	23	47
Sedentary behavior ≤ median	46	52	44	54	39	49	56	44	37	50
Physical activity ≤ median	49	54	44	56	58	52	39	61	57	63
Alcohol use										
Non drinkers	51	35	9	20	15	39	11	13	13	5
Occasional to weekly	39	46	64	56	50	57	77	65	73	84
Weekly to daily	10	20	27	24	34	4	12	22	13	11

Notes: BMI was categorized based on normal weight, overweight and obese BMI categories. Waist circumference, sedentary behavior and physical activity were categorized according to the median, which were 73.3 cm, 2.9 hours/day and 7.5 times/week respectively for female participants and 77.6 cm, 3,6 hours/day and 9.5 times/week for male participants. Number of cigarettes per day was categorized according to tertile in smokers: for female participants defined by 0.8 and 4.2 cigarettes per day and for male participants 0.7 and 5.7 cigarettes per day. Alcohol use was categorized according to past month frequency: 0 times/month non-drinkers, 0.1-7.9 times/month occasional to weekly, <8 times/month weekly/daily.

Table V: Body mass index (BMI) and waist circumference (WC) in males and females at age 17 and 24 years on average, and change in BMI and WC between age 17 and 24 years according to cannabis use. NDIT Study, 2005-2012.

Cannabis use (times/wk)	*Age 17 Mean (sd)*	*Age 24 Mean (sd)*	*Change age 17- 24 Mean (sd)*	*p-value*	*Age 17 Mean (sd)*	*Age 24 Mean (sd)*	*Change from age 17- 24 Mean (sd)*	*p-value*
	Male				***Female***			
	BMI (kg/m^2) *(n=271)*				**BMI (kg/m^2)** *(n=319)*			
Total	22.8 (3.8)	24.8(4.1)	2.0(2.5)		22.1(3.9)	23.7(4.6)	1.5(2.5)	
0	22.9(3.9)	25.5(4.4)	2.5(2.4)	0.002	22.2(3.6)	24.2(4.8)	1.8(2.6)	0.036
0.1	22.5(2.9)	24.4(3.6)	1.9(2.2)		21.5(3.6)	22.6(3.2)	1.1(2.4)	
0.4	23.2(4.1)	23.9(3.2)	0.8(1.8)		22.1(3.7)	22.8(4.3)	0.7(1.6)	
3	22.1(4.5)	23.4(4.1)	1.3(3.3)		22.0(3.4)	22.8(4.2)	0.8(1.9)	
7	22.9(3.9)	24.0(3.6)	1.1(2.5)		23.5(7.6)	24.8(7.0)	1.3(2.9)	
	WC (cm) *(n=250)*				**WC (cm)** *(n=283)*			
Total	79.8(9.4)	85.8(10.5)	5.8(7.2)		75.8(9.6)	77.6(11.3)	1.8(7.2)	
0	80.0(9.3)	86.8(10.9)	6.9(7.3)	0.066	75.6(9.2)	78.1(11.8)	2.5(7.8)	0.276
0.1	78.4(6.3)	84.5(9.2)	5.0(6.6)		75.4(9.4)	76.2(9.4)	0.9(6.2)	
0.4	80.5(10.7)	83.9(10.2)	2.6(3.9)		75.8(9.9)	76.5(11.8)	0.8(6.9)	
3	79.6(11.1)	83.9(10.9)	4.5(9.0)		77.1(9.0)	76.4(8.6)	-0.1(6.6)	
7	81.1(11.6)	86.0(9.8)	5.0(7.3)		78.1(15.7)	81.2(15.7)	2.9(5.7)	

Males

The interaction terms, "cannabis use and cigarette smoking", and "cannabis use squared and cigarette smoking", were statistically significant as was their joint effect in the BMI model (p=0.004) (Table VI, p.70; Appendix 2: Figure A. 6). In the WC model, the interaction term "cannabis use squared and cigarette smoking" was statistically significant, as were the combined pair of interactions (p=0.036) (Table VI, p.70; Appendix 2:Figure A. 6). In both models, the association between cannabis use and change in adiposity was U-shaped in non-smokers. In smokers, the plot became an inverted U-shape with increasing cigarette smoking (Figure 5.1 p.71). More specifically, among non-smokers, the adjusted mean change in BMI in cannabis non-users, weekly cannabis users and daily cannabis users was 2.4 kg/m^2(2.4,2.4), -0.2 kg/m^2(-0.2,-0.1) and 1.1 kg/m^2(-0.0,2.1), respectively. For hypothetical male participants who smoked 0.5 cigarettes per day, the predicted mean change in BMI in cannabis non-users, weekly cannabis users, and daily cannabis users was 2.4 kg/m^2(2.3,2.4), -0.1 kg/m^2(-0.1,0.0) and 1.1 kg/m^2(-0.2,2.3), respectively (Figure 5.1 p.71). For hypothetical male participants who smoked 15 cigarettes per day, the predicted mean change in BMI in cannabis non-users, weekly cannabis users, and daily cannabis users was 2.1 kg/m^2(1.9,2.4), 3.0 kg/m^2(2.5,3.5) and 1.6 kg/m^2(-5.1,8.5), respectively (Figure 5.1 p.71).

Similarly, among non-smokers, the adjusted mean change in WC among cannabis non-users, weekly cannabis users, and daily cannabis users was: 6.2cm (6.1, 6.2), 1.5cm (1.3,1.7) and 5.5cm (2.5,8.3) respectively. For hypothetical male participants who smoked 0.5 cigarettes per day, the predicated mean change in WC among cannabis non-users, weekly cannabis users, and daily cannabis users was

6.3cm (6.2,6.4), 1.9cm (1.6,2.1) and 5.5cm (2.0,9.0), respectively (Appendix 2: Figure A.3). The predicted mean change in WC for hypothetical male participants who smoked 15 cigarettes per day for cannabis non-users, weekly cannabis users, and daily cannabis users was: 8.2cm (7.1,9.3), 11.4cm (9.7,13.1) and 7.0cm (-14.9,29.0), respectively (Appendix 2: Figure A.3).

Three dimensional graphs of the models indicated that a stationary point existed at the intersection of the slopes of cigarette use and change in BMI or change in WC for cannabis non-users and weekly cannabis users. Solving the equations identified the point at which the association between cannabis use and change in BMI or change in WC flattened. For the model fitted to change in BMI, the point of intersection was at approximately 7 cigarettes per day, and for the model fitted to change in WC it was at approximately 10 cigarettes per day.

Females

Neither of the interaction terms, "cannabis use and cigarette smoking" or "cannabis use squared and cigarette smoking", were statistically significant in either the model for BMI or the model for WC in female participants. Although the beta coefficients for cannabis use and cannabis use squared were statistically significant (p=0.016 and, p=0.035, respectively) in the model testing change in BMI, the beta coefficients predicting change in WC were not statistically significant (p=0.149, and p=0.055, respectively). However, similar to the models for male non-smokers, the association between cannabis use and change in BMI was U-shaped. The adjusted mean change in BMI among cannabis non-users, weekly cannabis users, and daily

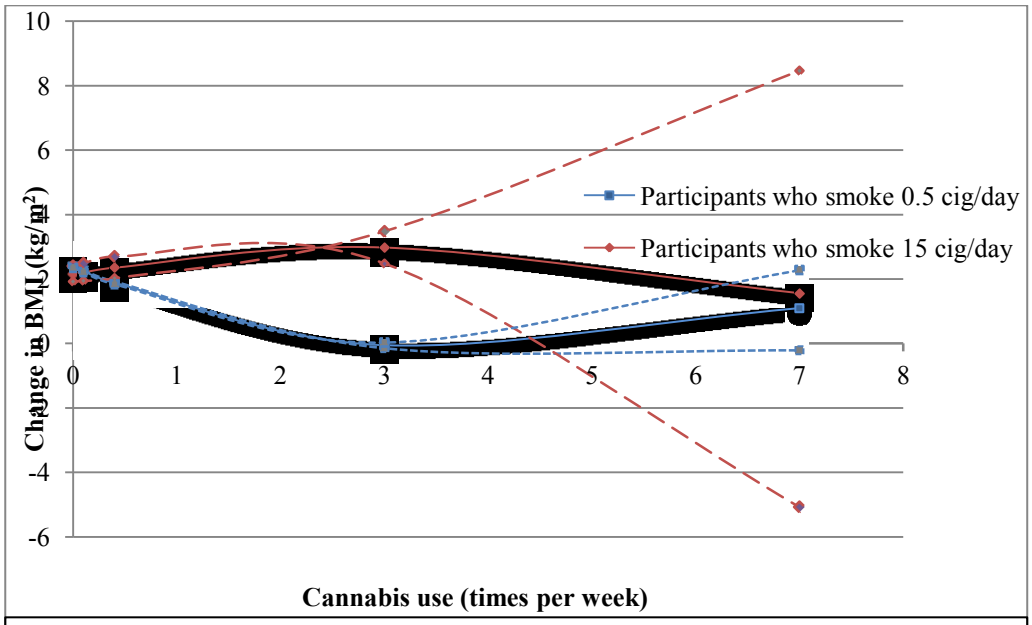
cannabis users were: 1.6 kg/m^2(1.5, 1.6), 0.4 kg/m^2(0.2,0.6) and 1.3 kg/m^2 (-1.6,4.1), respectively (Figure 5.2, p.71).

Table VI: Beta coefficients and 95% confidence intervals for the association between cannabis use (CU) and change in body mass index (BMI) (kg/m^2) and change in waist circumference (WC) (cm) in male and female participants. NDIT Study 2005-2012

	Change in BMI(kg/m^2)			**Change in WC (cm)**		
	Male					
	Model 1 β (95% CI)	**Model 2† β (95%CI)**	**Model 3† β (95%CI)**	**Model 1 β (95% CI)**	**Model 2† β (95% CI)**	**Model 3† β (95% CI)**
CU	-0.33* (-0.55,-0.11)	-0.41* (-0.63,-0.18)	-0.35* (-0.58,-0.13)	-0.28 (-0.95,0.38)	-0.68 (-1.14,0.02)	-0.47 (-1.20,0.26)
CU*CU	0.07 (-0.02,0.15)	0.09* (0.00,0.17)	0.08 (-0.00,0.16)	0.061 (-0.20,0.32)	0.16 (-0.09,0.41)	0.14 (-0.11,0.40)
Cigarette smoking		0.06 (-0.00, 0.11)	0.18* (0.08,0.28)		0.31* (0.11,0.50)	0.60* (0.31,0.90)
Cigarette smoking* CU			0.05* (0.02,0.08)			0.11 (-0.00,0.22)
Cigarette smoking* CU*CU			-0.02* (-0.03,-0.01)			-0.05* (-0.08,-0.01)
	Female					
	Model 1 β (95% CI)	**Model 2 β (95% CI)**	**Model 3 β (95% CI)**	**Model 1 β (95% CI)**	**Model 2 β (95% CI)**	**Model 3 β (95% CI)**
CU	-0.23* (-0.43,-0.02)	-0.26* (-0.47,-0.05)	-0.30* (-0.52,-0.07)	-0.47 (-1.16,0.23)	-0.52 (-1.23,0.19)	-0.73 (-1.47,0.02)
CU*CU	0.07 (-0.01, 0.16)	0.09* (0.01,0.17)	0.10* (0.01,0.18)	0.24 (-0.04,0.52)	0.27 (-0.01,0.55)	0.32* (0.04,0.60)
Cigarette smoking	-	0.01 (-0.06,0.08)	0.01 (-0.12,0.12)	-	0.06 (-0.16,0.27)	-0.15 (-0.51,0.21)
Cigarette smoking* CU	-	-	-0.02 (-0.06,0.02)	-	-	-0.10 (-0.23,0.02)
Cigarette smoking* CU*CU	-	-	-0.00 (-0.01,0.01)	-	-	0.03 (-0.06,0.07)

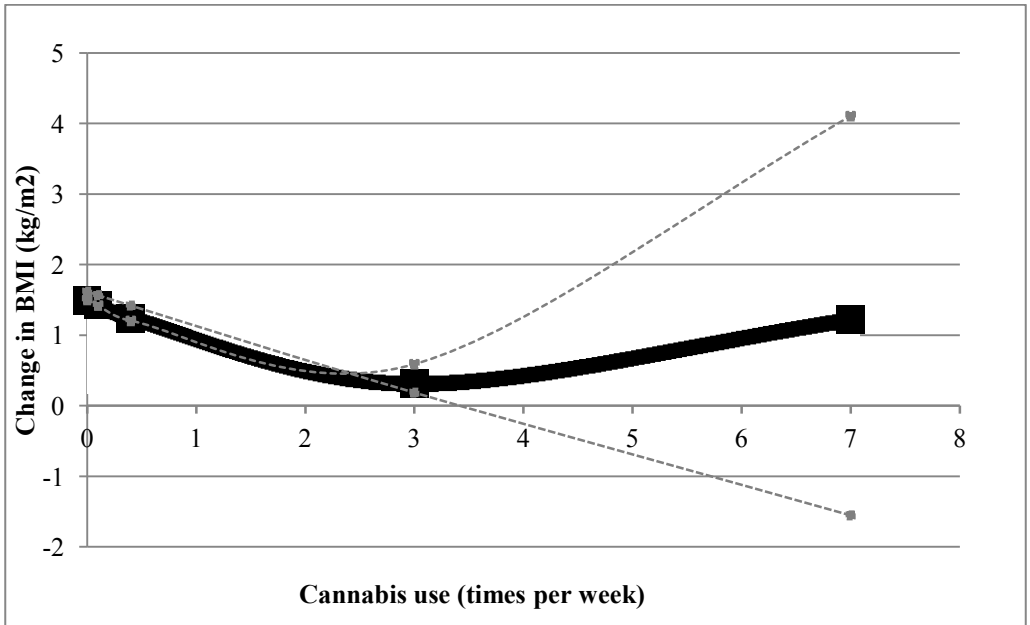
Model 1: unadjusted. Model 2: model adjusted for the baseline level of BMI or WC, physical activity and sedentary behavior. Model 3: model adjusted for the baseline level of BMI or WC, physical activity, and sedentary behavior. †For alcohol use. * $p<0.05$

Figure 5.1: Predicted change in BMI (kg/m^2) (95% confidence interval) according to cannabis use among hypothetical male participants who smoked 0.5 and 15 cigarettes per day, respectively



Models adjusted for baseline BMI, physical activity, sedentary behavior and alcohol consumption. Dashed lines indicate 95% confidence interval.

Figure 5.2: Predicted change in BMI (kg/m^2) (95% confidence interval) in female participants by cannabis use



Model adjusted for baseline BMI, physical activity and sedentary behavior. Dashed lines indicate 95% confidence interval.

Discussion

This study partially supports our hypothesis that cannabis use is associated with changes in adiposity (and more specifically with weight gain), and that this association is modified by cigarette smoking. As expected based on the literature, the association between cannabis use and change in adiposity differed between male and female participants. Among males, the association between cannabis use and change in adiposity was modified by cigarette smoking. A U-shaped association was observed among male non-smokers, while an inverted U-shaped association was observed in males who smoked more than approximately ten cigarettes per day. Among male participants, the smallest change in adiposity was observed among weekly cannabis users who were non-smokers; while, the largest change was observed in weekly cannabis users who smoked the most cigarettes.

In contrast, in females, neither of the interaction terms tested was statistically significant in either the model predicting change in BMI or the model predicting change in WC. Thus, it appears that the association between cannabis use and change in adiposity is not modified by cigarette smoking in females. The reduced models predicting change in BMI and change in WC according to cannabis use suggested a U-shaped association in females. However, only the model predicting change in BMI by cannabis use was statistically significant ($p<0.05$). Among females, the smallest change in BMI and WC was observed among weekly cannabis users. To the best of our knowledge this is the first time a population-based study has tested for effect modification in the association between cannabis use and change in adiposity by cigarette smoking in males and females.

The ECS is the biological framework used in this study to underpin our hypotheses about the association between cannabis use and change in adiposity and its interaction with cigarette smoking. The role of the ECS in energy homeostasis and its importance in regulation of feeding via hormones of the hypothalamus, have been documented and over-activation of the ECS is suggested as a potential cause of overweight and obesity (14, 16, 31, 33). In females and in male non-smokers who use cannabis three times a week or more, a positive association between cannabis use and change in adiposity is observed, which is consistent with studies that have demonstrated the orexogenic effect of cannabis. Our results are also consistent with studies that demonstrate that the effect of the ECS on energy homeostasis differs according to sex at a cellular level and at the endocrine level due to an interaction with the sex hormones (10-12). The homeostatic effects of the ECS have been found to be more apparent in males, while its effects on mood, particularly anxiety, are more apparent in females (10).

Two literature reviews that synthesized findings on the joint effects of cannabis and cigarette smoking identified cigarette smoking as an important modifier of the effects of cannabis use on the functioning of the ECS (19, 20). Most of the studies included in these reviews however, were animal studies and their applicability to human populations is not known. Contrasting and parallel effects of THC and nicotine highlighted in these reviews include their action on the reward system, substance initiation, cessation of substance use, and appetite (19, 20). The male-specific interaction between cannabis use and cigarette smoking observed in our

study partially supports the conclusions of these reviews and extends their applicability to the human population.

Population-based studies have examined the association between cannabis use and adiposity. In particular, two longitudinal studies have examined cannabis use and change in adiposity, but obtained conflicting results (24, 81). One study which was conducted in 1976 under ward condition (i.e., participants (all of whom were male) were restricted to a hospital area) showed that heavy cannabis users gained an average of 3.7 pounds (lbs), casual users gained 2.8 lbs and controls gained 0.2 lbs over a 21-day period of unlimited voluntary cannabis exposure (24). These results however should be interpreted with caution given the date of the study and the lack of replication of its findings. The other longitudinal study was the Coronary Artery Risk Development in Young Adults (CARDIA) study, which examined self-report cannabis use in relation to measured height, weight and WC controlling for gender, race, age, alcohol use, daily physical activity, physical fitness, education, income level and cigarette smoking. No independent association was observed between cannabis use and BMI or WC (81). This study did not consider possible sex differences in the association, nor did it examine possible effect modification of the association by cigarette smoking. Cross-sectional studies examining the association between cannabis use and BMI have generally shown either a negative or null association (4, 21-23, 25), and most of these studies also did not consider effect modification of the association by sex or by cigarette smoking.

Proposed mechanism

Three results of this study are particularly noteworthy. First, cigarette smoking in males modifies the association between cannabis use and change in adiposity. Second, there is a U-shaped association between cannabis use and change in adiposity in male non-smokers. Third, there is a U-shaped association between cannabis use and change in adiposity in females, which is statistically significant in the model fitted to change in BMI, but not in the model fitted to change in WC.

Physiological differences between the sexes at the level of the POMC synapse may explain the observed male-specific interaction (10). These synapses potentiate differently in male and female animals such that CB_1 activation result in increased excitation in females and in inhibition in males (10). POMC synapses are also influenced by nicotine through a nicotine receptor located on its membrane (98). It is therefore possible that nicotine and THC have interacting effects at the level of the POMC neurons in males, but not in females since CB_1 receptor density varies with the oestrous cycle in females and thus, may be more finely regulated (12). Further research is required to understand the sex specific interaction observed.

There is a U-shaped association between cannabis use and change in adiposity in male non-smokers, with the smallest change in adiposity observed in weekly cannabis users. Increased cannabis use among regular cannabis users (defined as weekly or more) may be associated with increased change in adiposity. Physiological data suggests that an increase in activity of the ECS results in increased appetite via the hypothalamus and its hormones such as leptin and NPY that are involved in digestion (16, 33). However, the U-shaped association observed in our study also

suggests that, compared to cannabis non-users, regular cannabis users have a smaller increase in adiposity. Genetic, neurobiological, social or behavioral differences in these two groups, rather than the difference in cannabis use, may explain these results. Given the expansive nature and role of the ECS in the body and the novelty of its discovery, an unknown confounder may have contributed to residual confounding of the association of interest.

The U-shaped association observed in this study may also be indicative of a hormesis phenomenon – a term used to describe an association in which the outcome is under homeostatic control and a physiological overcompensation occurs in response to an external stress in an effort to re-establish homeostasis (99). It can be hypothesized that at the periphery, stimulation by cannabinoids results in fat deposition and adipocyte differentiation, which are under negative feedback regulation by leptin (29). In weekly cannabis users, THC remains in the body stored in fat tissue and continues to stimulate the peripheral ECS (12). The increased peripheral adipose activity could result in increased leptin production which would decrease central energy storage behaviors. In daily users, high central and peripheral cannabinoid levels resulting from acute THC exposure would result in balanced down-regulation by leptin of peripheral and central endocannabinoids, and therefore no net change in adiposity would ensue. This hypothesis suggests that low levels of cannabis use may protect against increased weight gain in young adults.

Finally, the association between cannabis use and adiposity in females is U-shaped and only statistically significant in the model predicting change in BMI. Why the association differs between the WC and BMI models is unclear. The crude mean

change in WC (1.8cm) and its variance (7.5cm) in females suggests that the high variability of this measure may underpin the difference observed. In comparison, the mean change in BMI in females was of a similar magnitude (1.5 kg/m^2) with a smaller variance (2.5 kg/m^2). The proposed mechanisms for the U-shaped association between cannabis use and change in BMI in females may be similar to those described earlier for male non-smokers.

Limitations

The main limitation of this study is the self-report measure of cannabis use which may have resulted in information bias. Although we used a five point Likert-type response scale comparable to measures used in other population-based studies, its validity and reliability in the Canadian population is not known. A validation study was commissioned by the National Survey of Drug Use and Health in 2000-2001 in the U.S. that reports that the overall congruence between past-month recall and urinalysis is 90% (kappa=0.517, $p<0.001$) (100). However, these results were likely an over-estimation due to use of a population in which drug prevalence was low and its assumption that all individuals denying marijuana use in the past month and testing negative had in fact not used marijuana (101). No validation study has yet been conducted in Canada. Given the illicit nature of cannabis, cannabis use may have been under-reported.

Another possible source of information bias relates to the lack of data on mulling (i.e., mixing tobacco and cannabis together prior to smoking), which has not been quantified in North America. While mulling is a common practice in Europe, the extent to which cannabis users who do not smoke cigarettes are exposed to tobacco in

Canada remains unknown (88). If non-cigarette smoking cannabis users were exposed to tobacco through mulling, the associations observed would likely have been attenuated.

Finally, residual confounding may have biased the associations of interest. Genetics may differ in ECS at a receptor or signaling molecule level, thus altering both the homeostatic regulation of energy and the pre-disposition to cannabis use. Participants who smoke cannabis may control their weight more closely than those who do not use cannabis. Cannabis users may use greater amounts of other substances (i.e. other illicit drugs) that may alter energy homeostasis. Although the literature suggests that diet varies by both outcome and exposure, in the conceptual model used for this study, changes in diet as a result of cannabis use were viewed as being on the causal pathway between cannabis use and change in adiposity and was therefore excluded as a covariate. Age was also excluded from the analysis, since the cohort was from the same academic grade and therefore, there was little variability in age.

Conclusion

This study suggests that the association between cannabis use and change in adiposity is modified by cigarette smoking in males, but not in females. More specifically, the association was U-shaped in males who do not smoke cigarettes, while in male smokers, the association was an inverted U-shape. Male non-smokers who use cannabis weekly had the smallest adjusted change in adiposity. The largest change in adiposity was observed in weekly cannabis-users who also smoke cigarettes. Cannabis use in females was associated with change in adiposity in a U-

shaped relationship, with weekly cannabis users having the smallest adjusted change. This association was only statistically significant in the model predicting change in BMI. Increasing regular cannabis use was associated with an increased BMI, although the greatest increase in BMI was observed among cannabis non-users.

Chapter 6: Discussion

6.1. Summary of results

This study partially supports our hypotheses that cannabis use is associated with greater increases in adiposity over time; and that the association between cannabis use and change in adiposity is modified by cigarette smoking. The association between cannabis use and change in adiposity in males was modified by cigarette smoking. A U-shaped association was observed between cannabis use and change in adiposity in male non-smokers, while an inverted U-shaped association was observed in males who smoked more than approximately 10 cigarettes per day. The smallest change in adiposity was observed in male non-smokers who use cannabis weekly; while, the greatest change in adiposity was observed in males who used cannabis weekly and were smokers.

In contrast, in females, neither of the interaction terms tested was statistically significant in either the model predicting change in BMI or the model predicting change in WC. Thus, it appears that the association between cannabis use and change in adiposity is not modified by cigarette smoking among females. The reduced models (i.e., without the interaction terms) predicting change in BMI and change in WC according to cannabis use demonstrated a U-shaped association in females. However, only the model predicting change in BMI by cannabis use was statistically significant ($p<0.05$). Among females, the smallest change in BMI and WC was observed among weekly cannabis users.

6.2. The results in context

The ECS is the biological framework within which we conceptualized the association between cannabis use and change in adiposity, and its interaction with cigarette smoking. Studies examining the functions of the ECS in energy homeostasis demonstrate its role in the regulation of feeding via hormones of the hypothalamus, and have identified over-activation of the ECS as a potential cause of overweight and obesity (14, 16, 31, 33). The positive association between cannabis use and change in adiposity in females and in male non-smokers who use cannabis regularly is consistent with studies that report the orexogenic effect of cannabis use.

The functioning of the ECS differs according to sex at a cellular level and at the endocrine level due to an interaction with the sex hormones (10-12). Its homeostatic effects have been found to be more notable in males, while its effects on mood, particularly anxiety, are more notable in females (10). Two literature reviews that synthesized the joint effects of cannabis and cigarette smoking identified cigarette smoking as an important modifier of the effects of cannabis use on the ECS (19, 20). Most studies included in these reviews were animal studies and their applicability to human populations is not known. Contrasting and parallel effects of THC and nicotine highlighted in these reviews include their action on the reward system, substance initiation, cessation of substance use, and appetite (19, 20). The male-specific interaction between cannabis use and cigarette smoking observed in our study partially supports the conclusion of these reviews and extends their applicability to the human population.

Population-based studies have examined the association between cannabis use and adiposity. In particular, two longitudinal studies examined the association between cannabis use and change in adiposity, and obtained conflicting results (24, 81). One study which was conducted in 1976 under ward condition (i.e., participants (all of whom were male) were restricted to a hospital area) showed that heavy cannabis users gained an average of 3.7 pounds (lbs), casual users gained 2.8 lbs and controls gained 0.2 lbs over a 21-day period of unlimited voluntary cannabis exposure (24). These results should however be interpreted with caution given the date of the study and the lack of replication of the findings.

The second longitudinal study was the Coronary Artery Risk Development in Young Adults (CARDIA) study, which examined self-report cannabis use in relation to measured height, weight and WC, controlling for gender, race, age, alcohol use, daily physical activity, physical fitness, education, income levels and cigarette smoking. No independent association was observed between cannabis use and BMI or WC (81). This study did not examine possible effect modification of the association by sex or by cigarette smoking. Cross-sectional studies examining the association between cannabis use and BMI have generally shown either a negative or null association (4, 21-23, 25). Most of these studies also did not consider effect modification of the association by sex or by cigarette smoking.

6.3. Proposed mechanism

Three results of this study are particularly noteworthy. First, cigarette smoking in males modified the association between cannabis use and change in adiposity. Second, there was a U-shaped association between cannabis use and change in

adiposity in male non-smokers. Third, there was a U-shaped association between cannabis use and change in adiposity in females, which is only statistically significant in the model fitted to change in BMI.

Physiological differences between the sexes at the level of the POMC synapse may explain the observed male-specific interaction (10). These synapses potentiate differently in male and female animals such that CB_1 activation results in increased excitation in females and in inhibition in males (10). POMC synapses are also influenced by a nicotine through a nicotine receptor located on its membrane (98). It is therefore possible that nicotine and THC have interacting effects at the level of the POMC neurons in males, but not in females since CB_1 receptor density varies with the oestrous cycle and thus, may be more finely regulated in females (12). Further research is required to understand the sex interaction observed.

There was a U-shaped association between cannabis use and change in adiposity in male non-smokers, with the smallest change in adiposity observed in weekly cannabis users. Increased cannabis use among regular cannabis users (defined as weekly or more use) may be associated with increased change in BMI and WC. Physiological data suggests that an increase in activity of the ECS results in increased appetite via the hypothalamus and its hormones such as leptin and NPY that are involved in digestion (29, 33). However, the U-shaped association observed in our study suggests that, compared to cannabis non-users, regular cannabis users have a smaller increase in adiposity. Genetic, neurobiological, social or behavioral differences between these two groups, rather than the difference in cannabis use, may explain these results. Given the expansive nature and role of the ECS in the body and

the novelty of its discovery, an unknown confounder may have contributed to residual confounding of the association of interest.

The U-shaped association observed in this study may be indicative of a hormesis phenomenon – a term used to describe an association in which the outcome is under homeostatic control and a physiological overcompensation occurs in response to an external stress in an effort to re-establish homeostasis (99). It could be hypothesized that at the periphery, stimulation by cannabinoids results in fat deposition and adipocyte differentiation, which are under negative control by leptin (29). In weekly cannabis users, THC remains in the body stored in fat tissue and continues to stimulate the peripheral ECS (12). The increased peripheral adipose activity could result in increased leptin production which would decrease central energy storage behaviors. In daily users, high central and peripheral cannabinoid levels resulting from acute THC exposure would result in balanced down-regulation by leptin of peripheral and central endocannabinoids, and therefore no net change in adiposity would ensue. This hypothesis suggests that low levels of cannabis use may protect against increased weight gain in young adults. If this were the case, the long term effects of an overstimulation of leptin production should be examined.

Finally, the association between cannabis use and adiposity in females is U-shaped, and only significant in the model predicting change in BMI. Why the association differs between WC and BMI is unclear. The crude mean change in WC (1.8cm) and its variance (7.5cm) in females suggests that the high variability in this measure may underpin the difference. In comparison, the mean change in BMI in females was of a similar magnitude (1.5 kg/m^2) with a smaller variance (2.5 kg/m^2).

The proposed mechanisms for the U-shaped association between cannabis use and change in BMI in females may be similar to those described earlier for male non-smokers.

6.4. Limitations

This study was conducted as a secondary analysis of the larger NDIT study, the objectives of which did not include the objectives of this thesis. This analysis was therefore limited by the design of, and variables available in this larger data set. Its external validity was limited to the Montreal, Quebecois or Canadian young adult population due to the use of a convenience sample. However, efforts were made to ensure that the schools selected were representative of a diverse population.

The design of this study represents an unconventional straddling of the exposure by the baseline and final measures of the outcome variables as a consequence of the data available. Although this is atypical, the mean age of initiation to cannabis use in this population occurred prior to the first exposure and baseline outcome measure.

The main limitation of this study is the self-report measure of cannabis use which may have resulted in information bias. Although we used a five-point Likert-type response scale that is comparable to measures used in other population-based studies, its validity and reliability within the Canadian population is not known. The external validity of the studies outlined next is unknown since policies, law enforcement and social acceptability of cannabis use is differs by region.

Two studies were identified that compared test-retest reliability of self-report cannabis use. One study reported excellent test-retest concordance between self-report questions concerning lifetime, past-year and past-month cannabis use answered by Italian youth (aged 15-19) (Cohen's *k*= 0.862), which increased with age (102). Another study observed high concurrent validity between past six-months self-reported drug use and individuals' self-report Timeline Followback measure of use, a well-validated measure of illicit drug use, and the report of a spouse (98% and 86% agreement, respectively) (103). The sample of this study consisted of U.S. adults receiving couples treatment for one of the individual's alcohol problems.

Three studies compared self-report cannabis use measures to urinalysis measures. One study conducted in Chicago men (age 18-40 years) from the general population reported excellent concordance between a positive urine test and self-reported past-month marijuana use (kappa= .85) (104). A second study conducted in 248 U.S. adolescents observed only moderate concordance between urinalysis and self-reported measures (kappa=0.4) (105). Finally, a validation study was commissioned by the National Survey of Drug Use and Health in 2000-2001 in the U.S. that reports that the overall congruence between past-month recall and urinalysis is 90% (kappa=0.517, $p<0.001$) (100). These results were likely an over-estimation due to use of a population in which drug prevalence was low and its assumption that all individuals denying marijuana use in the past month and testing negative had in fact not used marijuana (101). No validation study has yet been conducted in Canada. Given the illicit nature of cannabis in Canada, cannabis use may have been under-reported in our study.

Another possible source of information bias relates to the lack of data on mulling (i.e., mixing tobacco and cannabis together prior to smoking), which has not been quantified in North America. While mulling is a common practice in Europe, the extent to which cannabis users who do not smoke cigarettes are exposed to tobacco in Canada remains unknown (88). If cannabis users who do not smoke cigarettes were exposed to tobacco through mulling, the associations observed in our study would likely have been attenuated.

The quality of the outcome measures, change in BMI and change in WC, are a strength of this study as a result of the standardized protocol used to collect them (50). The 189 imputed missing baseline BMI values reduced the quality of the BMI outcome measure, since these values were imputed from later self-report measures. However, in participants who were not missing measured BMI values, a high correlation was observed between the values predicted using self-report measures and their measured values.

Finally, residual confounding may have biased the associations of interest. Genetics may differ in ECS at a receptor or signaling molecule level, thus altering both the homeostatic regulation of energy and resulting in a pre-disposition to use cannabis. Participants who smoke cannabis may control their weight more closely than those who do not use cannabis. Finally, cannabis users may use greater amounts of other substances (i.e., other illicit drugs) that may alter energy homeostasis. Although the literature suggests that diet varies by both outcome and exposure in the conceptual model used for this study, changes in diet as a result of cannabis use may be on the causal pathway between cannabis use and change in adiposity and was

therefore excluded as a covariate. Age was also excluded from the analysis, since the cohort was from the same academic grade and therefore there was little variability in age.

6.5. Public health implications

The results of this thesis have public health implication related to the obesity pandemic and cannabis use. Although the mechanisms underpinning the associations observed have yet to be clarified, the results suggest that moderate cannabis use protects against weight gain, and may therefore have therapeutic potential in treating obesity. If this protective effect exists, the negative effects of cannabis use on health, particularly psychological, must be considered in any therapeutic strategy. In direct contrast, the results also indicate that regular cannabis use may be associated with increased weight gain. If cannabis use promotes weight gain, it may become a new target for obesity prevention and widespread dissemination of this information may discourage young adults who fear weight gain, from initiating cannabis consumption. If a U-shaped association between cannabis use and change in adiposity exists, it is possible to reconcile these contrasting results, by suggesting a “therapeutic” and a “toxic” range in cannabis use frequency. In such a case, synthetic cannabinoids could be used to treat obesity and cannabis could be targeted for prevention. The lack of research about the effects of cannabis use on health coupled with its widespread use is a major public health concern. Public health approaches to cannabis use prevention among Canadians may be needed, especially in parts of Canada where more youth are smoking cannabis than cigarettes (61). In order to support a public health approach, further research is necessary and a public discussion concerning the

legality of the drug needs development. Its illicit nature may relate at least in part to the lack of information about its effects in the population.

6.6. Future research

This study underscores that further research on cannabis use in the North American population is essential. Several key elements remain unresolved before results of this study can be considered robust. First, future research must use valid and reliable measures of cannabis use. For large scale studies, comparison of self-reports of cannabis use and urine tests in various age groups and regions is essential. Research is needed to quantify cigarette and cannabis co-use in the context of mulling or chasing. Does mulling occur as frequently in Canada as in Europe? Do individuals self-identify as tobacco smokers when they mull or chase? What are the patterns of use and simultaneous use? These issues need to be addressed in order to provide credibility to studies on cannabis use.

Our results suggest several avenues for further research. If there is an interaction between cannabis use and cigarette smoking in males and not in females, what aspect of the ECS is responsible for this? Is the mechanism for the interaction in males based on change in receptor density, affinity or activity alteration? Is the interaction in males the result of THC and nicotine acting centrally or peripherally? Are there unidentified factors that differentiate cannabis users from non-users that are responsible for the U-shaped associations observed? Would our results be replicable with repeated and more accurate measures of cannabis use? Given the novelty of this area of research and the results of this study, these are only a few of the many questions that remain to be answered.

Chapter 7: Conclusion

The current study was prompted by evidence that cannabis use has an effect on energy homeostasis. In males only, the effect of cannabis use on change in adiposity was modified by cigarette smoking, such that a U-shaped association was observed in non-smokers. The association in male smokers was also U-shaped but flattened and inverted with increasing cigarette use. The smallest adjusted change in adiposity was observed in males who did not smoke and who used cannabis weekly. The largest adjusted change was observed in males who used cannabis weekly and were smokers. Regular cannabis use was associated with increased adiposity. However, the largest increase in adiposity was observed in cannabis non-users.

In females, the association between cannabis use and change in adiposity was U-shaped. The association was statistically significant in the model predicting change in BMI, but not in the model predicting change in WC. In the BMI model, weekly cannabis users had the smallest adjusted change in BMI. Regular cannabis use was associated with increased BMI, although the largest increase in BMI was observed among cannabis non-users. Further population-based and neurobiological research is required to understand these differences in the associations across sex. It may also be necessary to consider exposure to cannabis in studies investigating the effects of cigarette smoking on energy homeostasis in males.

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APPENDICES

Appendix 1: NDIT questionnaire items for variables included in this thesis

Item from the maternal questionnaire:

1. What is the highest level of education that you have attained?

- ☐ Attended high school, but did not graduate
- ☐ Graduated from high school
- ☐ Attended CEGEP, community college, or technical program, but did not graduate
- ☐ Graduated from CEGEP, community college, technical program
- ☐ Attended university but did not graduate
- ☐ Graduated from university with a Bachelor degree
- ☐ Graduated from university with a Master's degree
- ☐ Graduated from university with a PhD
- ☐ Other (specify)_____

Items from survey cycles 1 to 20 questionnaires:

2. In what month is your birthday?

☐	January	☐	July
☐	February	☐	August
☐	March	☐	September
☐	April	☐	October
☐	May	☐	November
☐	June	☐	December

3. On what day of the month is your birthday? Circle the correct day.

1	2	3	4	5	6	7	8	9	10	
11	12	13	14	15	16	17	18	19	20	
21	22	23	24	25	26	27	28	29	30	31

4. In what year were you born?

- ☐ 1984
- ☐ 1985

- ☐ 1986
- ☐ 1987
- ☐ 1988
- ☐ Other _____

Specify year

5. How old are you today? Write the correct number in the box.

   ☐ years

6. Are you a…..?

   ☐ Boy ☐ Girl

7. What language do you speak most often at home? *Check ONE box.*

   - ☐ English
   - ☐ French
   - ☐ French and English
   - ☐ Other _____

   Specify

8. Were you born...?

   ☐ In Canada → _____

   Name province

   ☐ Outside Canada → _____

   Name country

9. Now, think about the physical activities that you did last week from Monday to Sunday <u>outside</u> your regular school gym class. For each activity that you did <u>for 5 minutes or more at one time</u>, mark an "X" to show the day(s) on which you did that activity.

	Mon.	Tues.	Wed.	Thur.	Fri.	Sat.	Sun.
Bicycling to school, bicycling to do errands, going for a bicycle ride							
Swimming/diving							
Basketball							

Baseball/softball							
Football							
Soccer							
Volleyball							
Racket Sports (badminton, tennis)							
Ice hockey/ball hockey							
Jump rope							
Downhill skiing, snowboarding							
Cross-country skiing							
Ice skating							
Rollerblading, skateboarding							
Gymnastics (bars, beams, tumbling, trampoline)							
Exercise / physical conditioning (push-ups, sit-ups, jumping jacks, weight-lifting, exercise machines)							
Ball-playing (dodge ball, kickball, wall-ball, catch)							
Track and field							
Games (chase, tag, hopscotch)							
Jazz/classical ballet							
Dancing (aerobic, folk, at a party)							
Outdoor play (climbing trees, hide and seek)							
Karate/ Judo/ Tai Chi/ Kung Fu							
Boxing, wrestling							
Outdoor chores (mowing, raking, gardening)							
Indoor chores (mopping, vacuuming, sweeping)							
Mixed walking / running / jogging							
Walking							
Running/Jogging							
Other(s) → Name them							
a)							

b)							
c)							

10. During the past 3 months, how often have you…?

	Never	Rarely	Sometimes	Often
Felt too tired to do things	☐	☐	☐	☐
Had trouble going to sleep or staying asleep	☐	☐	☐	☐
Felt unhappy, sad, or depressed	☐	☐	☐	☐
Felt hopeless about the future	☐	☐	☐	☐
Felt nervous or tense	☐	☐	☐	☐
Worried too much about things	☐	☐	☐	☐

11. During the past 3 months, how often did you…?

	Never	A bit to try	Once or a couple of times a month	Once or a couple of times a week	Usually every day
Drink alcohol (beer, wine, hard liquor)	☐	☐	☐	☐	☐

12. How many hours of television (including video movies) do you usually watch in a single day? *If the answer is zero, write "0" in the box. If the answer is less than ½ hour, write "LT ½".*

On weekdays, I usually watch ☐ hour(s) of television a day

On weekends, I usually watch ☐ hour(s) of television a day

13. How many hours do you usually play video or computer games, or use the Internet in a single day? *If the answer is zero, write "0" in the box. If the answer is less than ½ hour, write "LT ½".*

On weekdays, I usually play video or computer games …. ☐ hour(s) a day

On weekends, I usually play video or computer games …. ☐ hour(s) a day

Items from survey cycle 21 questionnaire:

14. In the past 12 months, how often did you …?

	Never	Less than once a month	1-3 times per month	1-6 times per week	Every day
Use marijuana, cannabis, hashish	☐	☐	☐	☐	☐

15. How much do you weigh?

pounds **OR** kilograms

16. How tall are you without your shoes on?

feet inches **OR** meters

17. Check the box that describes you best…

☐ I have smoked cigarettes, but not at all in the past 12 months
☐ I smoked cigarettes once or a couple of times in the past 12 months
☐ I smoke cigarettes once or a couple of times each month
☐ I smoke cigarettes once or a couple of times each week
☐ I smoke cigarettes every day

18. On how many days did you smoke cigarettes, even just a puff during the last month, which was (please type in month)? (for example, if this month is March, please answer the question for February)

☐ None → Go to question 21
☐ 1 day
☐ 2-3 days
☐ 4-5 days
☐ 6-10 days
☐ 11-15 days
☐ 16-20 days
☐ 21-30 days
☐ Every day
☐ Don't know

19. On the days that you smoked during the last month, which was (please type in month), how many cigarettes did you usually smoke each day? (for example, if this month is March, please answer the question for February)

- ☐ Less than 1 cigarette (one or a few puffs)
- ☐ 1 cigarette
- ☐ 2-3 cigarettes
- ☐ 4-5 cigarettes
- ☐ 6-10 cigarettes
- ☐ 11-15 cigarettes
- ☐ 16-20 cigarettes
- ☐ 21-25 cigarettes
- ☐ More than 25
- ☐ Don't know

20. On how many days did you smoke cigarettes, even just a puff during the month before the last, which was (please type in month)? (for example, if this month is March, please answer the question for January)?

- ☐ None → **Go to question 23**
- ☐ 1 day
- ☐ 2-3 days
- ☐ 4-5 days
- ☐ 6-10 days
- ☐ 11-15 days
- ☐ 16-20 days
- ☐ 21-30 days
- ☐ Every day
- ☐ Don't know

21. On the days that you smoked during the month before the last, which was (please type in month), how many cigarettes did you usually smoke each day? (for example, if this month is March, please answer the question for January)

- ☐ Less than 1 cigarette (one or a few puffs)
- ☐ 1 cigarette
- ☐ 2-3 cigarettes
- ☐ 4-5 cigarettes
- ☐ 6-10 cigarettes
- ☐ 11-15 cigarettes
- ☐ 16-20 cigarettes
- ☐ 21-25 cigarettes
- ☐ More than 25
- ☐ Don't know

22. On how many days did you smoke cigarettes, even just a puff during two months before the last, which was (please type in month)? (for example, if this month is March, please answer the question for December)?

- ☐ None → Go to question 25
- ☐ 1 day
- ☐ 16-20 days

- ☐ 2-3 days
- ☐ 4-5 days
- ☐ 6-10 days
- ☐ 11-15 days
- ☐ 21-30 days
- ☐ Every day
- ☐ Don't know

23. On the days that you smoked during two months before the last, which was (please type in month), how many cigarettes did you usually smoke each day? (for example, if this month is March, please answer the question for December)

- ☐ Less than 1 cigarette (one or a few puffs)
- ☐ 1 cigarette
- ☐ 2-3 cigarettes
- ☐ 4-5 cigarettes
- ☐ 6-10 cigarettes
- ☐ 11-15 cigarettes
- ☐ 16-20 cigarettes
- ☐ 21-25 cigarettes
- ☐ More than 25
- ☐ Don't know

24. Has a health professional ever diagnosed that you have any of the following? If yes, how old were you when first diagnosed?

	No	**Yes**	**First diagnosed when I was….**
Mood disorder (depression, bipolar disorder)	☐	☐	years old
Anxiety disorder (phobia, fear of social situations, obsessive-compulsive disorder, panic disorder, generalized anxiety disorder)	☐	☐	years old

Appendix 2: Figures pertaining to the univariate and multivariate analyses

Figure A.1: Mean change in waist circumference (cm) over seven years according to cannabis use in male participants, NDIT Study 2005-2012

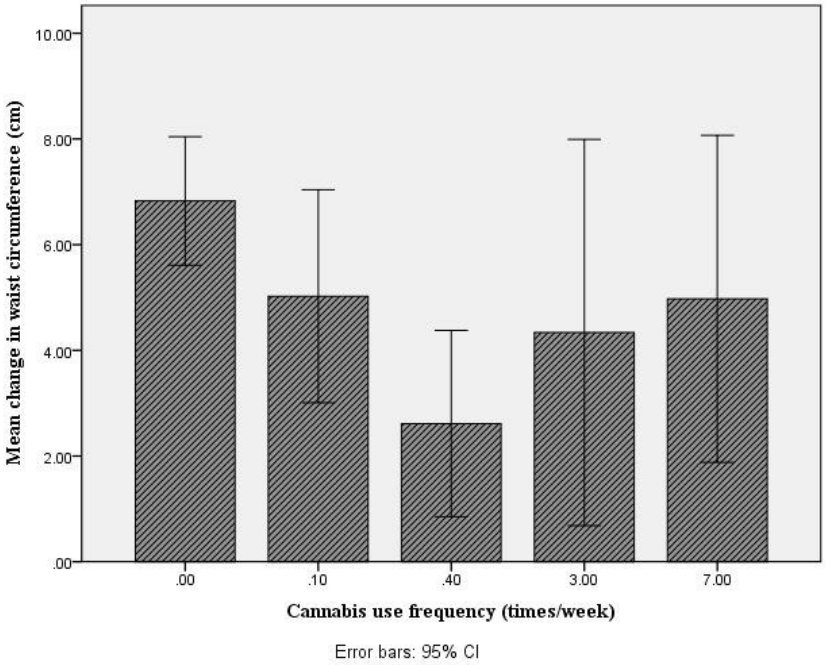


Figure A.2: Mean change in waist circumference (cm) over seven years according to cannabis use in female participants, NDIT Study 2005-2012

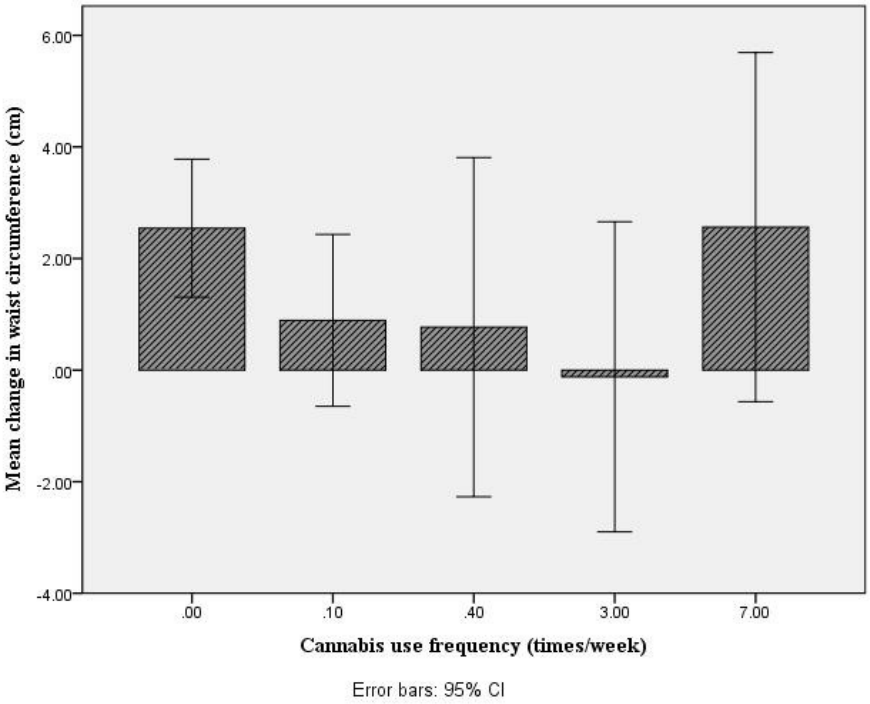


Figure A.3: Mean change in BMI (kg/m^2) over seven years according to cannabis use in female participants, NDIT Study 2005-2012

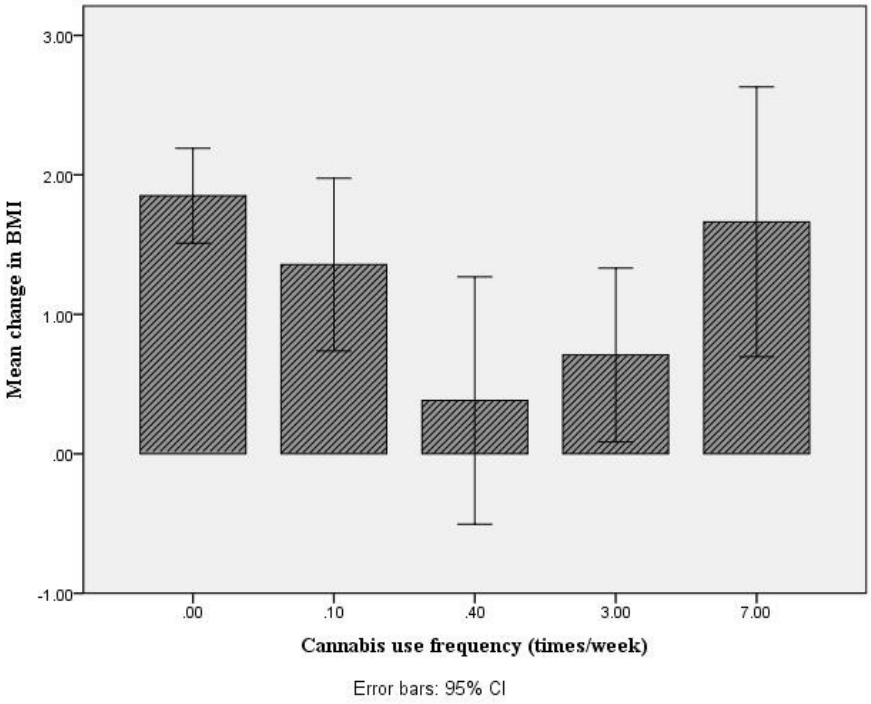


Figure A.4: Mean change in BMI (kg/m^2) over seven years according to cannabis use in male participants, NDIT Study 2005-2012

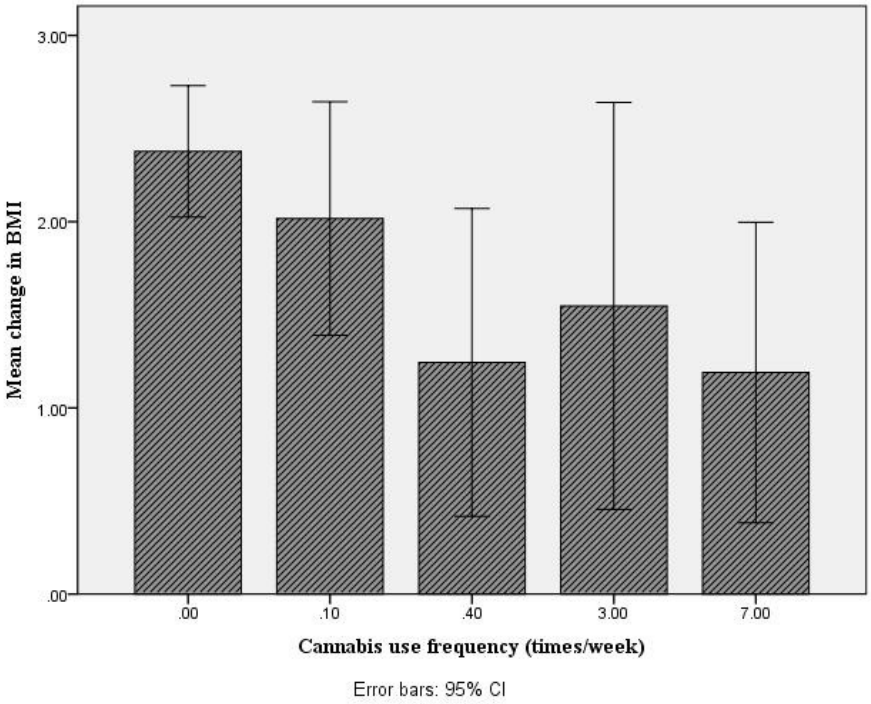
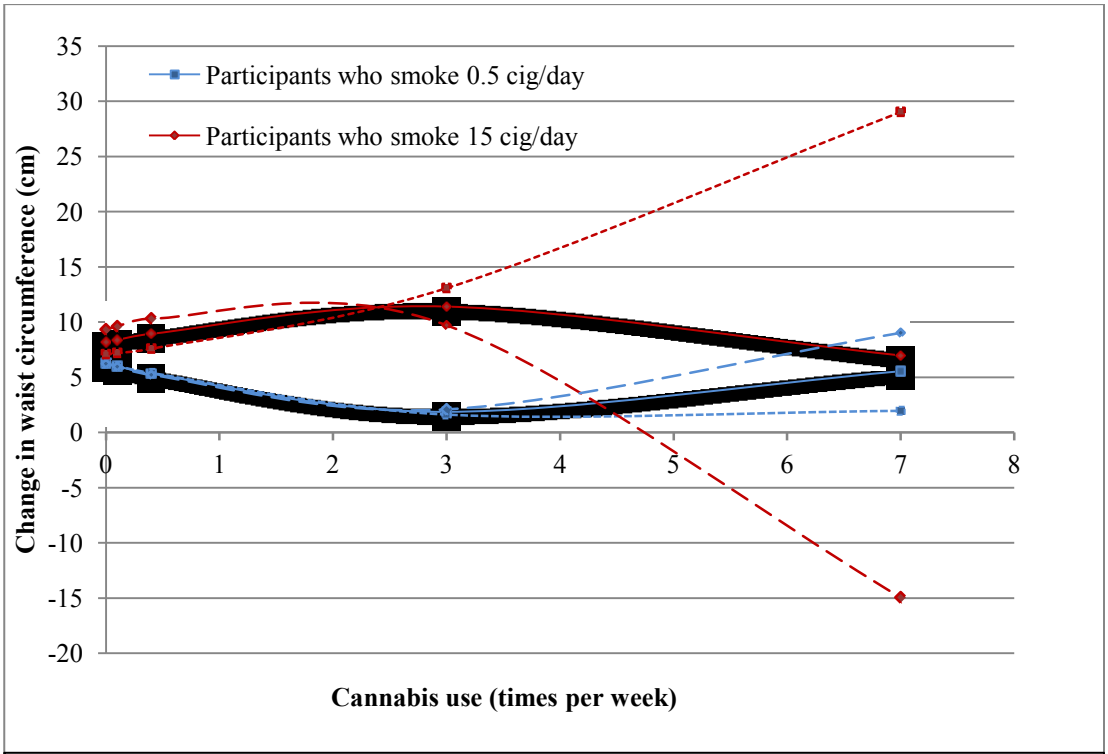


Figure A. 5: Predicted change in waist circumference (cm) (95% confidence interval) according to cannabis use in hypothetical male participants who smoke 0.5 and 15 cigarettes per day



Models adjusted for baseline BMI, physical activity, sedentary behavior and alcohol use.
Dashed lines indicate 95% confidence interval.

Figure A. 6: Likelihood ratio test: comparison of full and reduced regression models predicting change in BMI and WC in males

$$G^2 = -2\ln\left(\frac{likelihood\ for\ reduced\ BMI\ model}{likelihood\ for\ full\ BMI\ model}\right) \qquad G^2 = -2\ln\left(\frac{likelihood\ for\ reduced\ WC\ model}{likelihood\ for\ full\ WC\ model}\right)$$

$$G^2 = -2(-599.716 + 594.107) \qquad G^2 = -2(-834.683 + 831.357)$$

$$G^2 = 11.218, \mathrm{p} = 0.004 \qquad G^2 = 6.652, \mathrm{p} = 0.036$$

Appendix 3: Univariate analyses: extended tables

Table A.I: Change in BMI (kg/m^2) in male participants during young adulthood according to selected socio-demographic and lifestyle characteristics. NDIT Study, 2005-2012

Characteristic	*BMI at age 21 Mean (sd)*	*BMI at age 25 Mean (sd)*	*Change BMI Mean (sd)*	*p Value*
Age				0.168
≤ 20.3	22.4(3.7)	24.3(3.8)	1.8(2.1)	
> 20.3	23.1(3.9)	25.3(4.3)	2.2(2.8)	
Language				0.730
French	23.1(4.3)	25.4(4.8)	2.1(2.3)	
Other	22.6(3.6)	24.6(3.8)	2.0(2.6)	
Country of birth				0.064
Canada	22.8(3.9)	24.8(4.1)	1.9(2.4)	
Other	22.0(2.3)	25.0(2.9)	3.0(3.1)	
Maternal education				0.699
No university	23.0(4.1)	25.0(4.1)	1.9(2.8)	
Some university	22.6(3.6)	24.7(4.2)	2.1(2.2)	
Cannabis use				0.002
0 times/week	22.9(3.9)	25.5(4.4)	2.5(2.4)	
0.1 times/week	22.5(2.9)	24.4(3.6)	1.9(2.2)	
0.4 times/week	23.2(4.1)	23.9(3.2)	0.8(1.8)	
3 times/week	22.1(4.5)	23.4(4.1)	1.3(3.3)	
7 times/week	22.9(3.9)	24.0(3.6)	1.1(2.5)	
No. cigarette smoked/day				0.786
0	23.0(4.0)	25.2(4.1)	2.1(2.6)	
>0, ≤ 0.0822	21.8(2.7)	23.6(3.1)	1.8(2.3)	
>0.0822, ≤4.5	21.8(3.3)	23.6(3.4)	1.8(2.1)	
>4.5	23.9(4.2)	25.7(5.1)	1.8(2.7)	
Sedentary behavior				0.112
≤ 3.6 hours/day	22.5(3.9)	24.8(3.7)	2.3(2.2)	
> 3.6 hours/day	23.0(4.3)	24.9(4.5)	1.7(2.7)	
Physical activity				0.159
≤ 9.5 times/week	22.8(4.1)	24.7(4.2)	1.8(2.4)	
> 9.5 times/week	22.7(3.5)	24.9(4.0)	2.2(2.5)	
Depression symptom score				0.800
≤ 1.75	22.8(3.8)	24.8(4.0)	2.0(2.7)	
> 1.75	22.8(3.9)	24.8(4.2)	2.0(2.2)	
Alcohol use				0.261
Non drinkers	23.3(4.2)	25.1(4.5)	1.7(2.7)	
Occasional to weekly	22.5(3.7)	24.6(4.0)	2.1(2.4)	
Weekly to daily	22.8(3.8)	24.8(4.1)	2.0(2.5)	

Notes: Age was categorized according to the mean. BMI was categorized based on normal weight, overweight and obese BMI categories. Waist circumference, sedentary behavior, physical activity and depression symptoms were categorized according to the median. Number of cigarettes per day was categorized according to tertile in smokers. Alcohol use was categorized according to past month frequency: 0 times/month non-drinkers, 0.1-7.9 times/month occasional to weekly, <8 times/month weekly/daily.

Table A.II: Change in BMI (kg/m^2) in female participants during young adulthood according to selected socio-demographic and lifestyle characteristics. NDIT Study, 2005-2012

Characteristic	*BMI at age 21 Mean (sd)*	*BMI at age 25 Mean (sd)*	*Change BMI Mean (sd)*	*p Value*
Age				0.379
≤ 20.3	21.6(3.3)	23.1(4.2)	1.4(2.3)	
> 20.3	22.9(4.6)	24.5(5.0)	1.6(2.7)	
Language				0.294
French	22.6(4.7)	24.3(5.4)	1.7(2.6)	
Other	22.0(3.5)	23.4(4.2)	1.4(2.4)	
Country of birth				0.663
Canada	22.3(4.0)	23.8(4.7)	1.5(2.5)	
Other	20.4(2.5)	22.1(2.5)	1.7(2.1)	
Maternal education				0.364
No university	22.2(3.9)	233.8(4.9)	1.6(2.4)	
Some university	22.1(4.0)	23.4(4.0)	1.3(2.5)	
Cannabis use				0.036
0 times/week	22.2(3.6)	24.2(4.8)	1.8(2.6)	
0.1 times/week	21.5(3.6)	22.6(3.2)	1.1(2.4)	
0.4 times/week	22.1(3.7)	22.8(4.3)	0.7(1.6)	
3 times/week	22.0(3.4)	22.8(4.2)	0.8(1.9)	
7 times/week	23.5(7.6)	24.8(7.0)	1.3(2.9)	
No. cigarette smoked/day				.980
0	22.2(3.9)	3.8(4.8)	1.5(2.4)	
>0, ≤ 0.0822	22.0(3.2)	23.6(4.1)	1.5(2.2)	
>0.0822, ≤4.5	21.6(3.1)	23.0(4.0)	1.4(2.9)	
>4.5	22.8(5.8)	24.2(5.3)	1.4(2.7)	
Sedentary behavior				0.033
≤ 2.9 hours/day	21.8(3.1)	23.0(3.6)	1.2(2.3)	
> 2.9 hours/day	22.5(4.5)	24.3(5.4)	1.8(2.6)	
Physical activity				0.646
≤ 7.5 times/week	22.1(4.4)	23.5(4.9)	1.4(2.3)	
> 7.5 times/week	22.2(3.4)	23.8(4.4)	1.5(2.6)	
Depression symptom score				0.610
≤ 2.45	22.2(4.0)	23.7(4.8)	1.5(2.5)	
> 2.45	22.1(3.8)	23.6(4.4)	1.4(2.4)	
Alcohol use				0.977
Non drinkers	22.4(4.2)	23.9(5.1)	1.5(2.6)	
Occasional to weekly	21.9(3.7)	23.5(4.4)	1.5(2.4)	
Weekly to daily	22.9(4.9)	24.3(4.5)	1.4(2.2)	

Notes: Age was categorized according to the mean. BMI was categorized based on normal weight, overweight and obese BMI categories. Waist circumference, sedentary behavior, physical activity and depression symptoms were categorized according to the median. Number of cigarettes per day was categorized according to tertile in smokers. Alcohol use was categorized according to past month frequency: 0 times/month non-drinkers, 0.1-7.9 times/month occasional to weekly, <8 times/month weekly/daily.

Table A.III: Change in waist circumference (WC) (cm) in male participants during young adulthood according to selected socio-demographic and lifestyle characteristics. NDIT Study, 2005-2012

Characteristic	*WC at age 21 Mean (sd)*	*WC at age 25 Mean (sd)*	*Change WC Mean (sd)*	*p Value*
Age				0.217
≤ 20.3	79.2(9.9)	84.7(10.0)	5.2(6.8)	
> 20.3	80.5(8.7)	87.0(10.8)	6.4(7.7)	
Language				0.997
French	81.1(11.0)	86.7(12.4)	5.8(7.6)	
Other	79.3(8.6)	85.5(9.7)	5.8(7.1)	
Country of birth				0.051
Canada	80.0(9.5)	85.8(10.6)	5.5(6.9)	
Other	76.8(6.7)	85.8(8.6)	9.0(10.8)	
Maternal education				0.980
No university	80.3(10.6)	86.0(10.4)	5.8(7.8)	
Some university	79.6(8.3)	86.0(10.6)	5.8(6.7)	
Cannabis use				0.066
0 times/week	80.0(9.3)	86.8(10.9)	6.9(7.3)	
0.1 times/week	78.4(6.3)	84.5(9.2)	5.0(6.6)	
0.4 times/week	80.5(10.7)	83.9(10.2)	2.6(3.9)	
3 times/week	79.6(11.1)	83.9(10.9)	4.5(9.0)	
7 times/week	81.1(11.6)	86.0(9.8)	5.0(7.3)	
No. cigarette smoked/day				0.648
0	80.3(9.7)	86.5(10.7)	5.9(7.4)	
>0, ≤ 0.0822	78.0(7.3)	83.9(8.2)	5.1(7.2)	
>0.0822, ≤4.5	77.5(7.0)	83.2(7.8)	4.9(5.0)	
>4.5	82.3(11.9)	88.6(12.9)	7.0(8.3)	
Sedentary behavior				0.239
≤ 3.6 hours/day	78.9(7.6)	85.2(9.4)	6.4(6.8)	
> 3.6 hours/day	80.7(10.7)	86.4(11.3)	5.3(7.6)	
Physical activity				0.501
≤ 9.5 times/week	80.2(10.7)	85.7(10.8)	5.5(7.2)	
> 9.5 times/week	79.4(7.8)	86.0(10.2)	6.1(7.3)	
Depression symptom score				0.654
≤ 1.75	80.0(9.4)	85.6(10.6)	5.6(7.8)	
> 1.75	80.0(9.4)	86.0(10.4)	6.0(6.7)	
Alcohol use				0.701
Non drinkers	80.6(10.7)	86.5(11.6)	5.4(8.2)	
Occasional to weekly	80.0(9.0)	85.6(9.7)	5.8(6.6)	
Weekly to daily	77.3(5.9)	85.1(9.9)	6.6(6.7)	

Age was categorized by the mean of the cohort. BMI was categorized based on normal weight, overweight and obese BMI categories. Waist circumference, sedentary behavior, physical activity and depression symptoms were categorized based on the median. Number of cigarettes per day were split based on tertiles in smokers. Alcohol use was categorized according to past month frequency: 0 times/month non-drinkers, 0.1-7.9times/month occasional to weekly, <8times/month weekly/daily.

Table A.IV: Change in waist circumference (WC) (cm) in female participants during young adulthood according to selected socio-demographic and lifestyle characteristics. NDIT Study, 2005-2012

Characteristic	*WC at age 21 Mean (sd)*	*WC at age 25 Mean (sd)*	*Change WC Mean (sd)*	*p Value*
Age				0.607
≤ 20.3	75.2(9.0)	76.7(10.6)	1.6(7.4)	
> 20.3	76.5(10.3)	78.9(12.2)	2.1(7.0)	
Language				0.013
French	76.6(11.3)	79.8(13.5)	3.4(8.1)	
Other	75.4(8.8)	76.7(10.1)	1.1(6.7)	
Country of birth				0.358
Canada	76.1(9.7)	77.9(11.5)	1.7(7.3)	
Other	69.9(6.1)	73.9(6.6)	3.5(6.5)	
Maternal education				0.210
No university	75.9(9.8)	78.0(12.4)	2.3(8.0)	
Some university	76.0(9.6)	77.2(9.6)	1.2(6.3)	
Cannabis use				0.276
0 times/week	75.6(9.2)	78.1(11.8)	2.5(7.8)	
0.1 times/week	75.4(9.4)	76.2(9.4)	0.9(6.2)	
0.4 times/week	75.8(9.9)	76.5(11.8)	0.8(6.9)	
3 times/week	77.1(9.0)	76.4(8.6)	-0.1(6.6)	
7 times/week	78.1(15.7)	81.2(15.7)	2.9(5.7)	
No. cigarette smoked/day				0.674
0	75.6(9.5)	77.4(11.4)	1.4(6.7)	
>0, ≤ 0.0822	76.9(8.7)	78.3(10.6)	2.2(7.1)	
>0.0822, ≤4.5	74.0(7.3)	76.8(10.9)	2.8(8.3)	
>4.5	77.4(13.3)	79.3(12.9)	2.1(8.5)	
Sedentary behavior				0.081
≤ 2.9 hours/day	75.4(8.3)	76.3(9.5)	1.1(6.7)	
> 2.9 hours/day	76.2(10.8)	78.9(12.8)	2.6(7.7)	
Physical activity				0.951
≤ 7.5 times/week	75.6(10.6)	77.3(12.1)	1.8(7.1)	
> 7.5 times/week	76.0(8.5)	78.0(10.4)	1.8(7.4)	
Depression symptom score				0.869
≤ 2.45	76.1(9.9)	77.5(11.3)	1.7(7.4)	
> 2.45	75.4(9.3)	77.7(11.4)	1.9(7.1)	
Alcohol use				0.771
Non drinkers	76.0(10.2)	77.7(11.7)	2.3(7.3)	
Occasional to weekly	75.4(8.9)	77.5(10.8)	1.7(6.7)	
Weekly to daily	78.1(12.6)	78.7(13.9)	1.1(10.7)	

Age was categorized by the mean of the cohort. BMI was categorized based on normal weight, overweight and obese BMI categories. Waist circumference, sedentary behavior, physical activity and depression symptoms were categorized based on the median. Number of cigarettes per day were split based on tertiles in smokers. Alcohol use was categorized according to past month frequency: 0 times/month non-drinkers, 0.1-7.9times/month occasional to weekly, <8times/month weekly/daily.