CANNABIS AND MENTAL HEALTH

TEMPORAL TRENDS IN THE ASSOCIATION BETWEEN CANNABIS USE AND MENTAL HEALTH IN A NATIONALLY REPRESENTATIVE SAMPLE OF CANADIAN YOUNG AND OLDER ADULTS

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Lay Abstract

Using Statistics Canada data from the 2002 and 2012 Canadian Community Health Survey's Mental Health Component, this dissertation determines the strength of association between cannabis use and common mental health concerns including depression, anxiety, and suicide and the extent to which these associations have changed over time. Cannabis use was positively associated with emotional problems, and this association strengthened over time, particularly for depression and suicidal thoughts and attempts. These temporal associations were similar across age groups and for males and females, and remained after controlling for other substance use and socioeconomic status. These results add novel insights to the existing literature about the changing relationship between cannabis use and emotional problems over time and potential mechanisms of this change are discussed. Given the impending legalization of recreational cannabis in Canada, clinical and research implications of results are discussed at length.

Abstract

Background

With the impending legalization of recreational cannabis in Canada, it is important to examine the strength of association between cannabis use and common mental health concerns including depression, anxiety, and suicide and the extent to which these associations have changed over time. It is also important to examine the moderating effects of developmental age and biological sex on these associations.

Methods

This study uses Statistics Canada data from the 2002 and 2012 Canadian Community Health Survey's Mental Health Component (CCHS-MH) which represent repeated cross-sectional surveys from nationally representative samples of Canadians 15 years of age and older (2002 n=36,984; 2012 n=25,113). Step-wise multivariate analyses were performed using linear regression for psychological distress and binary logistic regression for Major Depressive Episode (MDE) and suicidal thoughts and attempts. Time was accounted for as a binary indicator (2002 vs. 2012) and an interaction term between cannabis use and time was added to all the models. Additional interaction terms were added to the models to test the moderating effects of cannabis frequency, developmental age, and biological sex. Sensitivity analyses were performed to adjust for other substance use and socioeconomic covariates. Weighting and bootstrapping was utilized to present results reflective of the Canadian population.

Results

Cannabis use was positively associated with emotional problems, and this association strengthened over time, particularly for depression and suicidal thoughts and attempts. These temporal associations were similar across age groups and for males and females, and remained after controlling for other substance use and socioeconomic status.

Conclusions

Findings provide a baseline assessment of the Canadian population prior to legalization and direction for health promotion and prevention campaigns. Results highlight the need for awareness and regular monitoring of the co-occurrence of cannabis use and emotional problems and offer guidance for future research.

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List of Abbreviations and Symbols

AIC = Akaike's Information Criterion
BIC = Bayesian Information Criterion
CBD = Cannabidiol
CCHS-MH = Canadian Community Health Survey's Mental Health Component
CI = Confidence Interval
CUD = cannabis use disorder
DSM = Diagnostic Statistical Manual
ECS = Endocannabinoid System
FDR = False Discovery Rate
GLM = Generalized Linear Model
ICD-10 = International Classification of Diseases
K10 = Kessler-10
LFS = Canadian Labour Force Survey
MCAR = Missing Completely at Random
MDE = Major Depressive Episode
NOS = Newcastle-Ottawa Scale
OR = Odds Ratio
aOR = Adjusted Odds Ratio
SCID = Structured Clinical Interview for the Diagnostic Statistical Manual
SD = Standard Deviation
SE = Standard Error
SES = socioeconomic status
SFS = Subjective Financial Situation
SUD = Substance Use Disorder
THC = delta-9-tetrahydrocannbinol
US = United States
Var = Variance
VIF = Variance Inflation Factor
WHO WMH CIDI = World Health Organization World Mental Health Composite International Diagnostic Interview
φ =Phi correlation
n = sample size
r = Pearson correlation coefficient
r_{pb}=Point Biserial correlation

Declaration of Academic Achievement

This dissertation is a secondary analysis of the Statistics Canada Canadian Community Health Survey's Mental Health Component from 2002 and 2012. This dissertation determined the strength of the association between cannabis use and emotional problems in the Canadian population and that this association was strengthening over time. This analysis was conceived of, designed, conducted, interpreted, prepared, and disseminated by the student with guidance from Dr. Katholiki Georgiades (primary supervisor) and committee members including Dr. Michael Boyle, Dr. Catharine Munn, and Dr. Susan Jack. Dr. James MacKillop also provided valuable feedback particularly regarding the background and conceptualization of the analysis. This work was completed between June 2016 and May 2018. As such, all the work contained herein meets the requirements for inclusion in the manuscript of a Master's of Science dissertation.

Chapter One: Introduction

Psychiatric disorders, particularly depression, anxiety, and substance use disorders, are the leading cause of morbidity worldwide (Whiteford et al., 2013). During emerging adulthood (aged 15-24 years), approximately 10-20% of individuals in North America will experience a psychiatric disorder, with suicide being one of the leading causes of death among this population (Canadian Mental Health Association, 2017; Institute for Health Metrics and Evaluation, 2016; Pearson, Janz, & Ali, 2013). The likelihood of experiencing a substance use problem is doubled among those who experience another psychiatric disorder, otherwise known as a concurrent disorder or dual-diagnosis, with this overlap being the highest during emerging adulthood (Rush et al., 2008).

Globally, cannabis is the most commonly used illicit substance, with use most prevalent among emerging adults (Canadian Centre on Substance Abuse, 2016b; National Institute on Drug Abuse, 2016; Schulenberg et al., 2017; Statistics Canada, 2015; United Nations, 2017). Canadian youth report the highest rates of use compared to youth in other European and North American countries (Currie, 2012). Cannabis use is positively associated with mental illness and suicidal behaviours (Lev-Ran, 2013). The composition of recreational cannabis appears to play a role in the association between use and mental health concerns and this composition has changed significantly over the last decade in the illicit market (Cascini, Aiello, & Di Tanna, 2012). Few studies are positioned to be able to examine trends in the association between cannabis use and mental health over time, and temporal changes have not been examined in the Canadian context. With the impending legalization of recreational cannabis in Canada (Government of Canada, 2017), it is important to examine the strength of association between cannabis use and common mental health concerns and the extent to which this association has changed over time.

Brief Overview of the Biochemistry of Cannabis

Marijuana is the common name for a specific species of cannabis called *Cannabis sativa* (Health Canada, 2013). Cannabis is a plant composed of over 500 different compounds including a class of chemicals called cannabinoids (ElSohly, Radwan, Gul, Chandra, & Galal, 2017). The most studied cannabinoids include THC (delta-9-tetrahydrocannbinol) and CBD (Cannabidiol) (ElSohly et al., 2017). THC and CBD appear to have opposing psychological effects. Using products high in THC have demonstrated increases in anxiety and psychosis, while CBD has shown to decrease anxiety by impacting signalling in multiple pathways involved in anxiety processes and dampening of THC's psychoactive effects (Atakan et al., 2013; Health Canada, 2013). Marijuana, or *Cannabis sativa*,

is the species of cannabis with naturally higher levels of THC (Atakan et al., 2013).

THC and CBD, as well as the other cannabinoids in marijuana, act on the body's endocannbinoid system (ECS) (Health Canada, 2013). The ECS is broadly distributed throughout the body, producing a wide range of physiological and psychological effects including effects on neurodevelopment, memory and cognition, emotionality and learning, and modulation of dopamine-reward pathways (Health Canada, 2013; Solinas, Tanda, Wertheim, & Goldberg, 2010; Volkow, Hampson, & Baler, 2017). Our body produces its' own endogenous cannabinoids that play a critical role in the maintenance of homeostatic neuronal activity. Exogenous cannabinoids, such as the psychoactive ingredient in cannabis (THC), stay in our system much longer than our body's endogenous cannabinoids and they are not regulated by our brain's homeostatic mechanisms. Therefore, repeated administration of THC, being exogenous and external to homeostatic processes, results in a new "normal" for the ECS, altering the structure of the ECS to accommodate the constant stimulation. This tolerance effect, or down-regulation, puts people at a greater risk for mental health concerns (Tambaro, Tomasi, & Bortolato, 2013; Volkow et al., 2017).

How is Cannabis Changing?

Composition. The amount of THC, the psychoactive component, in recreational cannabis has been significantly increasing over the past decade. A systematic review of THC content from 1979 to 2009 in Europe and North America found mean THC has increased 4.7% (Cascini, Aiello, & Di Tanna, 2012). Cannabis seized by the Drug Enforcement Administration (DEA) in the United States (US) has shown increases in THC content from approximately 4% in 1995 to 7% in 2002 to 12% in 2012-2014, while CBD has decreased from approximately 0.5% in 2002 to 0.2% in 2002 to <0.2% in 2014 (ElSohly et al., 2016). In 2016, a biochemical analysis of 12 popular recreational strains of cannabis in Toronto, Canada revealed an absence of CBD entirely (CBC Marketplace, 2016). Even an analysis of current Health Canada licenced medical cannabis, which is sometimes obtained for recreational use, found that most medical products were THC dominant (65%), with 91% of these products only containing trace amounts of CBD (<1%) and 58% containing more than 15% THC (Mammen, de Freitas, Rehm, & Rueda, 2017). Given the differential effects of THC and CBD, these changes might reflect changes in the magnitude of association between cannabis and mental illness over time.

Legalization. In various parts of the world, cannabis is being decriminalized, legalized for recreational purposes, and legalized for medicinal

purposes. Canada legalized medical cannabis in 1999 with multiple changes in policy over the years (Health Canada, 2016). The number of Canadians with authorization to possess cannabis for medical purposes has dramatically increased from 605 individuals in 2003 to 28,076 in 2012 to 98,000 registered users in September 2016 and now over 235,000 (unpublished health Canada data; Health Canada, 2018). This increase has occurred despite the limited evidence of the effectiveness of medical marijuana for many of the conditions for which it is being prescribed. Recreational cannabis in Canada is estimated to become legal in 2018 (Government of Canada, 2017).

Little is known about the sequelae of events that will follow legalization. In the US, a survey of young adults revealed 40% of cannabis users and 9.5% of non-users stated they would use cannabis more regularly if it were legalized. More importantly, about 20% of individuals experiencing current symptoms of depression or anxiety stated they had intentions to use cannabis more frequently once it was legalized (Cohn, Johnson, Rose, Rath, & Villanti, 2017). Among Ontario students in grades 9-12, 53% reported that they did not intend to use cannabis even once it is legalized; 15.1% were not sure; 15.9% stated they would use as often as they do now; 10.3% reported intentions to try it; and 4.9% reported the intention to use more often (Boak, Hamilton, Adlaf, & Mann, 2017). Although studies exist on the effects of decriminalization and legalization in other countries, Pacula and Smart (2017) highlighted the difficulties in generalizing evidence from existing studies on legalization due to the heterogeneity in the populations, in the cannabis products (i.e. smoked, edibles, etc.) and actual laws (i.e. decriminalization, medical legalization, recreational legalization, and the policies surrounding those laws).

Cannabis and mental illness trends. Few population studies that are repeated over time allow us to investigate temporal changes in the association between substance use and mental illness. The National Survey on Drug Use and Health (NSDUH) in the US compared rates of co-occurring substance use and other types of mental illnesses over time, although changes in measures limit long-term comparability (Center for Behavioral Health Statistics and Quality, 2015). This study found that, between 2008-2014, there has been a significant decrease in the prevalence of concurrent disorders (any mental illness, assessed by the Structured Clinical Interview for Diagnostic Statistical Manual (DSM) 5, and a Substance Use Disorder [SUD]) among 18-25 year olds, no difference in 26 to 49 year olds, and an increase in 50 year olds and older. Among youth 12-17 years, this study found that the prevalence of co-occurring SUDs and Major Depressive Episode (MDE) was similar from 2006 to 2014 but lower than 2004 and 2005. These results are limited in a number of ways, including: (a) not delineating the

prevalence rates for specific substances (i.e. cannabis) or specific mental illnesses (except MDE in adolescents); (b) measuring mental illness differently in adults and adolescents, limiting ability to determine age effects; and (c) measuring mental illness and SUD using different measures over time, including in 2015, limiting comparability of new rates with older prevalence estimates. Although this dataset provided opportunities for more in-depth examination into specific mental illnesses and SUDs, these questions have not yet been examined and changes in measurement may inhibit the ability to appropriately compare over a longer period of time. Moreover, given this data comes from a US sample, the results may not be generalizable to the Canadian context.

Cannabis During Emerging Adulthood

In Canada, prevalence of cannabis use has been fluctuating but in general trending downward, particularly among emerging adults with prevalence estimates of past year use declining from 37% in 2004 to 20% in 2012 and 25% in 2015 (Government of Canada, 2014; Statistics Canada, 2015). Among adolescents, the prevalence of past year cannabis use has gone from about 29% in 2001 to 20% in 2017 among grades 7-12 students, while past year use has gone from 43.5% in 2001 to 36.9% in 2017 among grade 12 students (Berg et al., 2015; Boak, Hamilton, Adlaf, & Mann, 2015; Johnston, O'Malley, Bachman, Schulenberg, & Miech, 2015). Despite this decline, cannabis use in emerging adults remains almost three times higher than that of the adult population, with approximately 25.5% of emerging adults reporting past year use compared to 9.9% of older adults (Canadian Centre on Substance Abuse, 2016a). Additionally, Canadian youth report the highest rates of use among 43 North American and European Countries (Currie, 2012). This is particularly concerning as the ECS is integral to proper neurodevelopment (Long, Lind, Webster, & Weickert, 2012) and, during adolescence, the brain undergoes significant 'rewiring' (Arain et al., 2013; Dow-Edwards & Silva, 2017). The adolescent brain is not fully developed until approximately 25 years of age (Gavin, MacKay, Brown, & al., 2009), with the prefrontal cortex (involved in decision making, planning, higher order thinking) being the last area of the brain to reach full maturity (Arain et al., 2013). During adolescence, repeated and frequent administration of exogenous cannabinoids, like THC, has demonstrated a disruption of normal neuronal development (Dow-Edwards & Silva, 2017) including changes in the structure and function of the brain (Jacobus, Squeglia, Infante, Bava, & Tapert, 2013; Jacobus et al., 2015; Jacobus, Squeglia, Sorg, Nguyen-Louie, & Tapert, 2014; Medina, Nagel, Park, McQueeny, & Tapert, 2007; Shollenbarger, Price, Wieser, & Lisdahl, 2015; Zalesky et al., 2012). If THC is the primary component of cannabis negatively influencing the ECS and brain development, the increasing

potency of THC in recreational cannabis may be resulting in increasing deleterious effects of cannabis on emerging adults. This may include greater changes in the brain associated with emotionality, dopamine-reward systems, and down-regulation of endogenous receptors.

Biological Sex Effects of Cannabis

Biological sex differences have also been consistently documented, with males more likely than females to use any substance, to have a poly-substance use disorder, and to experience dependence (NIDA; SAMHSA, 2014b). Females have been shown to develop a physiological dependence more quickly than males (Hernandez-Avila, Rounsaville, & Kranzler, 2004) accompanied by higher degrees of subjective craving (Fox, Morgan, & Sinha, 2014; Hitschfeld et al., 2015; Kennedy, Epstein, Phillips, & Preston, 2013; Robbins, Ehrman, Childress, & O'Brien, 1999), greater severity of withdrawal symptoms (Sherman et al., 2017), and are more likely to experience relapse (Kippin et al., 2005; Rubonis et al., 1994). Specifically looking at cannabis use disorder (CUD), females and males who use cannabis are at equal risk of developing a concurrent disorder (i.e. substance use disorder with a comorbid mental illness), although females with CUD appear more vulnerable to experiencing suicidal ideation and hospitalizations from suicide attempts (du Roscoat, Legleye, Guignard, Husky, & Beck, 2016; Foster, Li, McClure, Sonne, & Gray, 2016), anxiety symptoms (Buckner et al., 2012; Buckner, Mallott, Schmidt, & Taylor, 2006; Foster et al., 2016), and psychological distress at follow up (Danielsson, Lundin, Allebeck, & Agardh, 2016a). Cannabis use is also more strongly associated (in a dose-dependent trend) with lower quality of life in females with anxiety disorders (Lev-Ran, Le Foll, McKenzie, & Rehm, 2012), females with depressive disorders (Aspis et al., 2015), and healthy females (Lev-Ran, Imtiaz, et al., 2012).

Biological sex differences in the effects of cannabis have been hypothesized to be due in part to differences in expression of sex hormones (Craft, Marusich, & Wiley, 2013; Craft, Wakley, Tsutsui, & Laggart, 2012; Fattore et al., 2007; Fattore, Spano, Altea, Fadda, & Fratta, 2010; Winsauer et al., 2011), the function of the ECS (Krebs-Kraft, Hill, Hillard, & McCarthy, 2010; Winsauer et al., 2011), and/or biological differences in the dopamine system (i.e. number of neurons, density of terminals, and responsiveness of the dopamine system to drugs) which is further differentially influenced by estrogen (Becker, Perry, & Westenbroek, 2012; Fattore, Melis, Fadda, & Fratta, 2014; Moran-Santa Maria, Flanagan, & Brady, 2014). Assuming THC plays a role in the interplay between cannabis, biological sex, and mental illness, it is possible that the increasing amount of average THC in recreational cannabis may have greater impact on females than males.

What Do We Currently Know About The Association Between Cannabis Use And Depression, Anxiety And Suicidal Ideation And Behaviours?

Depression. In a Canadian population sample, cannabis dependence is significantly higher in individuals with major depression (5.1% lifetime dependence, 2.9% past year dependence) in comparison to those without depression (1.4% lifetime dependence, 0.4% past year dependence) (Patten et al., 2015). In 2014, Lev-Ran and colleagues conducted a meta-analysis of longitudinal studies that controlled for depressive symptoms at baseline, which found that individuals who ever used cannabis had 1.17 times the odds (95% CI 1.05-1.30) of developing depressive symptoms while individuals who used at least once per week had 1.62 times the odds (95% CI 1.21-2.16) of developing new depressive symptoms compared to non-users or occasional users (Lev-Ran et al., 2014). Since this review, several recent longitudinal studies have found evidence that cannabis use is associated with increases in depressive symptoms (Danielsson, Lundin, Allebeck, & Agardh, 2016b; Feingold, Weiser, Rehm, & Lev-Ran, 2015; Henchoz et al., 2016) while other studies have failed to find a significant association between cannabis use and subsequent onset of depression (Blanco et al., 2016a; Danielsson, Lundin, Agardh, Allebeck, & Forsell, 2016b; Feingold et al., 2015; Hill, 2017). Despite the lack of agreed-upon sequence of events, recent studies consistently find a cross-sectional association between cannabis use and depressive symptoms (Danielsson, Lundin, Agardh, Allebeck, & Forsell, 2016a). As noted by Lev-Ran et al. (2014) there are inconsistencies in the way studies operationalize cannabis use and depression as well as variability in the number and type of confounders, making it difficult to compare study results. Additionally, Lev-Ran found studies on average did not meet criteria for high methodological rigor based on the Newcastle-Ottawa Scale (NOS), although this tool has unreliable quality estimates (Hartling et al., 2013; Lo, Mertz, & Loeb, 2014). Therefore, although two systematic reviews (Lev-Ran et al., 2014; Patten et al., 2015) report a positive association between use and onset of depression, recent observational studies have produced mixed results due in part to methodological quality and methodological differences.

Anxiety. A meta-analysis of 31 studies found a moderate positive association between anxiety and cannabis use (OR 1.68 [95% CI 1.23, 2.31]) and CUD (OR 1.68 [95% CI 1.17, 2.40]) in the general population (Kedzior & Laeber, 2014). Five of the included studies examined cannabis and anxiety longitudinally while controlling for psychiatric and demographic confounders, and found a longitudinal effect indicating higher cannabis use at baseline led to increased odds of experiencing anxiety at follow-up that was small in magnitude (OR 1.28 [95% CI 1.06, 1.54]) (Kedzior & Laeber, 2014). A more recent meta-analysis of

longitudinal studies also found a significant association between baseline cannabis use and later anxiety (OR 1.15 [95% CI 1.03, 1.29]) but this association was rendered non-significant when the analysis was restricted to only high quality studies (Twomey, 2017). Since these reviews, one study reported a positive longitudinal association (Danielsson, Lundin, Allebeck, et al., 2016a), two studies failed to find associations between cannabis use at baseline and increased odds of developing anxiety symptoms (Blanco et al., 2016b; Danielsson, Lundin, Agardh, et al., 2016a), and one study found mixed results in terms of direction and strength of association depending on the type of anxiety disorder (Feingold, Weiser, Rehm, & Lev-Ran, 2016). Overall, the direction and strength of association between cannabis use and anxiety disorders remains unclear. In examining the methodological rigor of the studies, it should be noted that Kedzior and Laeber (2014) did not perform an assessment of the quality of included studies. Twomey (2017) found only half of included studies met criteria for high methodological rigor according to the NOS (which, as noted above, may not be a reliable tool), and stated results should be interpreted with caution due to mixed study quality. In summary, the meta-analyses suggest there is an association between cannabis use and anxiety disorders and cannabis use may precede the development of anxiety disorders, however, the causal nature of these associations remains unclear.

Suicide. A recent review on cannabis use and suicide found that, among existing longitudinal and case-control studies, chronic cannabis use at any frequency increased the odds of experiencing later suicidal ideation (OR 1.43 [95% CI 1.13, 1.83], moderate effect) and suicide attempts (OR 2.53 [95% 1.00-6.39], large effect) (Borges, Bagge, & Orozco, 2016). In individuals who used cannabis 'heavily' (considering high number of times ever used and/or high frequency of use), these estimates were much higher for both suicidal ideation (OR 2.53 [95% CI 1.00, 6.39]) and attempts (OR 3.20 [95% CI 1.72, 5.94]) (Borges et al., 2016). They noted a lack of existing evidence examining the extent to which acute cannabis use might increase immediate risk of suicidal behaviours. This review pointed towards cannabis use, particularly heavy cannabis use, increasing the likelihood of later suicidal ideation and attempts, although confidence intervals reflect some uncertainty around the magnitude of these effects. Additionally, authors note small sample sizes, heterogeneity of included studies, publication bias, and lack of consistent adjustment of key variables (e.g. depression and alcohol use) limit confidence in results. A more recent body of literature has continued to suggest associations between cannabis and suicidal behaviours, as well as bi-directional temporal associations between cannabis use or general substance use and suicidal behaviours in various populations (Agrawal et al., 2017; Bohnert, Ilgen, Louzon, McCarthy, & Katz, 2017; Borges, Benjet,

Orozco, Medina-Mora, & Menendez, 2017; Elgin, 2015; Kimbrel, Meyer, DeBeer, Gulliver, & Morissette, 2017; Kimbrel, Newins, et al., 2017; Ostergaard, Nordentoft, & Hjorthoj, 2017; Shalit, Shoval, Shlosberg, Feingold, & Lev-Ran, 2016; Weeks & Colman, 2017; Youssef, Fahmy, Haggag, Mohamed, & Baalash, 2016). To date, there has been no systematic assessment of the methodological rigor or quality of studies on cannabis and suicide. Overall, the existing body of evidence supports a consistent association between suicidal ideation/attempts and cannabis use, with evidence to suggest longitudinal bidirectional relationships between cannabis use and suicidal behaviours, particularly use preceding suicidal behaviours. However, caution is needed when interpreting these findings due to a lack of quality assessments and presence of publication bias. Additionally, the main predictor of suicidal behaviours is depression, and suicidal ideation is a symptom of depression (Gould et al., 1998; Reinherz et al., 1995); although most studies adjust for depression, this potential indirect association between cannabis use, depression, and suicidal behaviours has not been explicitly examined.

Limitations of Existing Literature

There are several notable limitations to the existing epidemiological literature examining the association between cannabis use and mental illness. Methodological concerns include inadequate operationalization of cannabis and inconsistent adjustment of confounding variables. First, cannabis use is often inadequately operationalized with much of the existing literature dichotomizing cannabis use. This only allows for the exploration of any use versus no use, potentially underestimating associations and limiting the ability to make appropriate inferences given that evidence consistently suggests that frequent use is most concerning (Hall, 2015; Lev-Ran et al., 2014). Although most existing epidemiological data are limited to number of days of use at minimum regular or frequent use should be differentiated from experimental or occasional use. In addition, confounding variables are inconsistently addressed, particularly in the anxiety and depression literature. Reviews highlight the importance of controlling for socio-demographic characteristics, alcohol, and other substance use disorders that are associated with both cannabis use and mental health concerns, often attenuating the effect size (Borges et al., 2016; S. Lev-Ran et al., 2014). Failure to control for confounding variables may lead to misattribution.

Additionally, older studies may not be applicable given the changes in cannabis over in terms of composition (increasing THC), social acceptance, and the legal status of the drug both medically and recreationally (Berg et al., 2015; Boak, Hamilton, Adlaf, & Mann, 2015; Johnston, O'Malley, Bachman, Schulenberg, & Miech, 2015; Okaneku, Vearrier, McKeever, LaSala, & Greenberg, 2015; SAMHSA, 2014a), making it difficult, if not impossible, to use

studies from several years ago to draw conclusions about recreational cannabis and mental health disorders currently. Lastly, few studies have examined the extent to which developmental period and biological sex act as moderators on the association between cannabis use and mental illness although limited existing neurobiological and epidemiological evidence suggest that they do. The identification of effect modifiers provides opportunities to test the extent to which findings generalize to important sub-groups of the population of interest. To my knowledge, no studies have examined if the strength of the association between cannabis and mental health concerns has changed over time and if developmental age and biological sex moderate a temporal change.

Current Study and Relevance of Study Findings

Overall, there is a relatively strong evidence base documenting a consistent cross-sectional association between recreational cannabis and depression, anxiety, and suicide. The longitudinal evidence is much weaker but some studies suggest cannabis use precedes the development of depressive symptoms and suicidal behaviours. This association appears to be stronger for specific aspects of use (i.e. time of initiation, duration of use, frequency of use) and potentially biological sex (i.e. females appearing worse off than males). See Figure 1 for a summary of the literature and the analytic framework that will guide the current study.

While much of the existing literature has focused on examining longitudinal associations between cannabis use and mental illness, few studies have documented temporal trends in the strength of these associations. Apart from the NSDUHS in the US, few population studies are positioned to track changes in the association between cannabis use and mental health concerns over time. With recreational cannabis legalization set to be implemented by 2018 in Canada, further research is needed to quantify the magnitude of association between cannabis use and common mental health concerns, such as anxiety, depression, and suicide and the extent to which these associations have changed over time. Further, by considering developmental period and biological sex, the findings of this study will provide insights into the social and neurobiological risk factors influencing temporal associations between cannabis use and mental health outcomes (Refer to Figure 1).

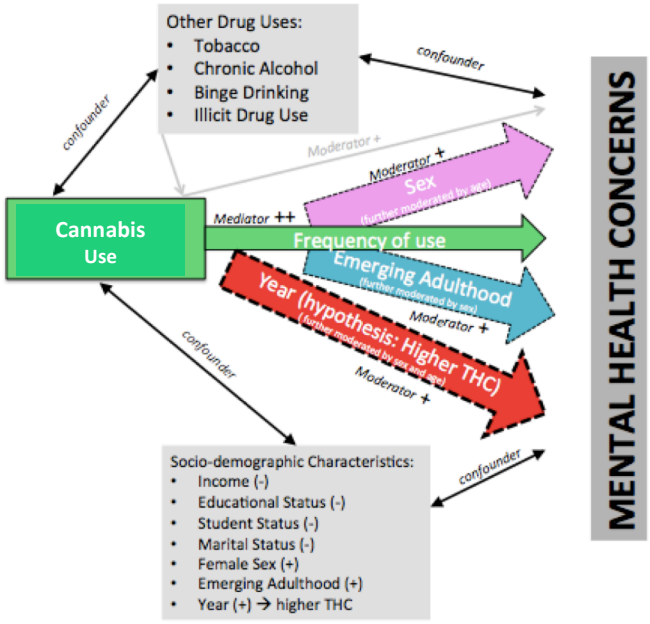
The findings of this study will provide important information to facilitate primary, secondary, and tertiary prevention strategies as well as to inform policy and future research. A strong univariate relationship between frequency of use and mental health outcomes, independent of the presence or absence of moderating effects, may provide support for increased screening of substance use

and concurrent disorders in primary care and counselling centres, as well as highlighting the importance of integrating substance use and mental illness treatment. Moderating effects may highlight the need for more targeted approaches for females or specific developmental periods. These findings may also inform future iterations of the Canadian Lower Risk Cannabis guidelines (Fischer et al., 2017) regarding frequency of use and special populations. The results of temporal trends may inform how contextual factors associated with time, such as the evolution of federal legislation and changing chemical composition of recreational cannabis, have previously impacted Canadians; although these attributions will be speculative since we are unable to directly measure contextual effects over time. Overall, this study will provide a foundation for future examination of substance use patterns and associations with common mental health outcomes as the cannabis culture evolves in Canada. However, it is important to note that this study is based on cannabis use in an illegal market, but these relationships may change with legalization.

If this study finds evidence to support that the association between cannabis use and negative mental health outcomes adjusted for developmental age and biological sex has increased meaningfully from 2002 to 2012, recommendations may include: studying the effects of cannabis potency on mental health more in depth, informing medical cannabis prescribing practices (i.e. screening questions before prescribing a high THC product), providing guidance for public health campaigns (i.e. discussing risks of use which may or may not be different depending on age or gender). If gender and/or developmental age moderate the relationship, Canadian Lower Risk Guidelines may need to be re-evaluated to reflect potential risk factors for particular patterns of use, as they do not currently discuss gender and only discuss age in terms of age of initiation.

If an association is found between use and mental health outcomes, and this effect does not change over time, we may hypothesize that either: 1) the THC content in both 2002 and 2012 was sufficient enough be associated with mental health problems, but that this was not a dose-response relationship where higher potency was associated with an even higher likelihood of mental health disorders or; 2) another component of cannabis may be involved in the psychological effects of cannabis that has remained stable over time, and/or; 3) the mental health outcomes may be due to the act or behaviour of using as opposed to the actual biochemical composition.

Figure 1. Analytic framework summarizing the literature review.



Research Questions & Hypotheses

Question 1

Has the strength of association between cannabis use and major depressive episodes, psychological distress, and suicidal behaviours, changed between 2002 and 2012?

Hypothesis 1. Since the composition of cannabis has changed over time, with the average THC content of recreational cannabis rising, the magnitude of the cross-sectional association between cannabis use and mental health concerns is expected to increase over time.

Question 2

Does developmental age moderate this temporal association?

Hypothesis 2. It appears that initiating regular use during adolescence is associated with a greater risk of experiencing negative consequences, particularly

due to the effect of THC on the ECS and maturing brain. Due to the increase in average THC and interplay with the developing brain, it is hypothesized that there will be a stronger association between cannabis use and emotional concerns among emerging adults in 2012 compared to 2002.

Question 3

Does biological sex moderate this temporal association?

Hypothesis 3. From existing literature, it appears that females experience more negative outcomes than males in regards to cannabis use. Assuming THC plays a role in the interplay between cannabis, sex, and mental health outcomes, it can be hypothesized that an increasing amount of average THC in recreational cannabis may be impacting females more so than males. Therefore, it is hypothesized that the association between cannabis use and mental health will be strengthening over time more so for females than males who use cannabis.

Question 4

Does this temporal association remain after controlling for alcohol and other illicit substance use?

Hypothesis 4. Alcohol use and illicit substance use have previously demonstrated significant associations with mental health outcomes. Given cannabis use rarely occurs in isolation, it is suspected that effect sizes will be attenuated with the addition of other substance use variables in the model but statistical significance will be retained.

Question 5

Does this temporal association remain after controlling for socio-demographic characteristics?

Hypothesis 5. Given the complexity of mental health and substance use concerns, it is hypothesized that effect sizes will be attenuated with the addition of socio-demographic characteristics but statistical significance of the associations will remain.

Question 6

Does the temporal association remain after controlling for smoking frequency in the 2012 sample?

Hypothesis 6. Given tobacco use has an independent link to mental illness and there is an overlap between cannabis use and smoking, it is hypothesized that effect sizes will be attenuated with the addition but statistical significance of the associations will remain (Kalman, Morissette, & George, 2005; Korhonen, Ranjit, Tuulio-Henriksson, & Kaprio, 2017).

Chapter One References

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Chapter Two: Methods

This chapter will provide an overview of the data, variables, and methodology to address the study objectives outlined in Chapter One. This study is a secondary analysis of pre-existing nationally representative cross-sectional surveys conducted by Statistics Canada. In addition to describing the design and sampling approach of the surveys, the measures used, and the analysis plan, this chapter also discussed methodological issues associated with controlling for confounding, weighting and bootstrapping, multiple testing, and interpreting clinically meaningful results.

Design and Sampling

This study uses Statistics Canada data from the 2002 and 2012 Canadian Community Health Survey's Mental Health Component (CCHS-MH) which represent repeated cross-sectional surveys of nationally representative samples of Canadians 15 years of age and older. The CCHS-MH provides information regarding mental health and functioning, substance use, service use, and socio-demographic variables. This is an occasional survey that has only been conducted twice (2002 and 2012) with no indication of another round of data collection. The surveys were developed in collaboration with Health Canada and the Public Health Agency of Canada, the Provincial Health Ministries, the Mental Health Commission of Canada, and academic experts and underwent pilot qualitative and quantitative testing (Statistics Canada, 2003, 2013). As a cross-sectional study, all variables were measured at one point in time to document the national prevalence of mental health concerns and associated correlates. The sampling approach and application of survey weights allow for generalizability of this data to the Canadian population (Tabachnick & Fiedell, 2013). Due to the cross-sectional design, causality cannot be inferred, and therefore, the analysis focuses on prevalence, the strength of associations, and population changes (Tabachnick & Fiedell, 2013). However, the repeated population based survey design allows us to determine change in the strength of associations over time, but not the exact mechanisms contributing to these temporal changes.

CCHS-MH samples excluded individuals who were living on reserves or other aboriginal settlements, employed full-time in the Canadian Forces, or institutionalized (~2-3% of the Canadian population) (Statistics Canada, 2003, 2013). The Canadian Labour Force Survey (LFS) (Statistics Canada, 2018) was used as the sampling frame for the CCHS-MH. A multi-stage stratified cluster sampling design was used to select respondents by sampling: (a) geographical clusters or regions, (b) households, and (c) a single individual per household taking into account sex, age and socioeconomic status (SES) (with some

oversampling of particular age groups in 2002). In 2002, there was an 86% (n=41,560) household response rate, 89% (n=36,984) individual response rate, and a combined Canadian response rate of 77%. In 2012, there was a 79.9% household response rate (n=29,088), 86.3% individual response rate (n=25,113) creating an overall response rate of 68.9% (Statistics Canada, 2003, 2013). Data were collected primarily using computer-assisted interviewing (CAI) by trained Statistics Canada interviewers. Interviews were standardized to allow for a systematic approach to data collection and to reduce interviewer bias. In 2012, 87% of the interviews were conducted in person in the individuals' homes and in 2002 86% were completed in person. All other interviews were conducted over the telephone. Data from the 2002 and 2012 CCHS-MH were pooled for comparative purposes.

Measures

The CCHS-MH in 2002 and 2012 were not identical surveys, as both surveys were attempting to address the time-dependent gaps in knowledge and policy implications, but efforts were made to preserve the comparability of key measures across time periods. Measures of Psychological Distress (Kessler-10 [K10]) and Major Depressive Episode (MDE) had no changes across the two survey years (i.e., 2002 and 2012). The suicide module had very minor changes in 2012 that corrected for an incorrect skip pattern in 2002. Statistics Canada implemented an imputation scheme to address the incorrect skip in 2002 (described in detail below). Substance use was measured in two ways: (a) frequency of use, including cannabis use, which is comparable between 2002 and 2012, and (b) substance abuse/dependence which are not comparable due to major changes in items between survey years. See Table 1 for the variable coding schemes.

Substance use.

Past year cannabis frequency. Cannabis use frequency is presented as a triad of questions including:

1. Have you ever tried marijuana (yes=1, no=0)?
2. Have you used marijuana in the past 12 months (yes=1, no=0)?
3. How often did you use marijuana in the past 12 months (less than once a month, 1 to 3 times, once a week, more than once a week, everyday)?

Responses to the three questions were combined to create a measure of past month use and coded as follows: '0' never, '1' less than once a month, '2' 1 to 3 times a month, '3' once a week, '4' more than once a week, and '5' every

day. Preliminary analyses were conducted with each response option retained but subsequently response options were collapsed to increase the power of the analysis. Preliminary analyses revealed overlapping confidence intervals for any monthly use, and therefore, for the main analyses in this study, cannabis use is captured as at least monthly use '1' (combination of 2 to 5) and less than monthly or never use '0' (combination of 0 and 1).

Past year alcohol involvement. Individuals were asked: in the past 12 months:

1. Have you had an alcoholic beverage (yes=1, no=0)?
2. How often do you drink alcoholic beverages (response options included less than once a month, once a month, 2 to 3 times a month, once a week, 2 to 3 times a week, 4 to 6 times a week, or every day)?
3. How often do you have 5 or more drinks in one sitting (response options included never, less than once a month, once a month, 2 to 3 times a month, once a week, more than once a week)?
4. To capture number of drinks: in 2002, participants were asked During the past 12 months, did you regularly drink more than 12 drinks a week (yes or no); while in 2012 participants were asked How many drinks do you usually have per drinking day (user defined numeric value)?

The Canadian Low Risk Drinking Guidelines (for adults) provides criteria for acute and chronic alcohol consumption. Acute problematic consumption (also known as binge drinking) is defined as 5 or more drinks in a sitting (Bondy et al., 1999). Acute use was captured by item 3 in both 2002 and 2012. Acute use was measured ordinally from '0' never to '5' and treated continuously in the analyses. Chronic problematic consumption is defined as more than 10 drinks per week for females and 15 for males (Bondy et al., 1999). Chronic uses was measured differently in 2002 compared to 2012. In 2002, chronic use was captured by a single question (item 4). To create a comparable binary measure for 2012, I multiplied item 2 (how often do you drink) by item 4 (number of drinks) to determine total number of drinks typically consumed per week and determined if the number of drinks was '0' less than 12 per week or '1' 12 or more per week. Since item 3 had categorical response options, the weekly number of drinks was calculated for both the lower and upper limits of item 3 response options. Prevalence of chronic use (binary) in 2002 was compared to estimates of chronic use in 2012 using both lower and upper bounds. Upper limits of the 2012 categories (i.e. 3 days and 6 days per week) yielded similar levels of chronic use to 2002 (2002 7.99%; 2012 using lower limits 5.36%; 2012 using upper limits

7.93%), and therefore, chronic use calculated with the upper limits was used in the analyses.

Present smoking. Smoking cigarettes was only assessed in 2012. Individuals were asked:

1. Have you ever smoked a whole cigarette (yes=1, no=0)?
2. At present, do you smoke cigarettes daily, occasionally or not at all?

Present smoking was captured as 0 'never', 1'occasional', or 2 'daily'.

Other illicit substance involvement. For each individual illicit substance, participants were asked a triad of questions regarding cocaine, amphetamines, ecstasy/methylenedioxymethamphetamine[mdma], hallucinogens, solvents, and heroin use including:

1. Have you ever tried (substance of interest)?
2. Have you used (substance of interest) in the past 12 months?
3. How often did you use (substance of interest) in the past 12 months?

Frequency is broken down into 6 categories: nonuser, less than once a month, 1-3 times a month, once a week, more than once a week, every day. A binary variable was created to capture the presence or absence of past year use of any illicit substance other than marijuana, coded as '0' never or not in the past 12 months, or '1' use of any other illicit substance in the past 12 months.

Structured diagnostic interview for MDE. MDE was assessed using the World Health Organization World Mental Health Composite International Diagnostic Interview (WHO WMH CIDI, 2017). The CCHS-MH surveys captured past year MDE as defined by the DSM-IV including required symptom counts, evidence of clinically significant distress and/or impairment and excluding symptoms explained by bereavement. Measurement was identical between 2002 and 2012. This measure has moderate concordance with the Structured Clinical Interview for the Diagnostic Statistical Manual (SCID) (Area Under the Curve 0.75). It is a conservative estimate of MDE, at times underestimating the prevalence of MDE when compared to the SCID (as per McNemar's tests) (Haro et al., 2006). MDE was captured as '0' no and '1' meets criteria for MDE in the past 12 months.

Past year suicidal thoughts and attempts. Individuals were asked a series of questions regarding suicidal thoughts and attempts in the last 12 months: Have you thought about committing suicide or taking your own life, and if so,

have you attempted suicide or tried to take your own life? Based on frequency of reporting, suicidal thoughts and attempts were collapsed into '0' no and '1' endorsed suicidal thoughts and/or attempts in the past 12 months.

Psychological distress. The Kessler-10 (K10) is a 10-item self-report questionnaire that measures past month psychological distress. Response options follow a Likert scale of 0 *"none of the time"* to 4 *"all of the time"*. Scores are summed, 0 to 40, with higher scores reflective of greater distress. It is a reliable measure, with excellent internal consistency (Cronbach *a*=0.919 to 0.93) (Cornelius, Groothoff, van der Klink, & Brouwer, 2013; Kessler et al., 2002; Kessler et al., 2003; Thomas et al., 2016). It also demonstrates criterion validity: good sensitivity (81 to 85% for scores >17 and >27 respectively) and specificity (83%) (Andrews & Slade, 2001; Huang, Xia, Sun, Zhang, & Wu, 2009) for mood and anxiety disorders when compared to other measures of distress, disability, impaired functioning and diagnostic interviews. This measure also demonstrates good to excellent discriminant validity for mood and anxiety disorders assessed by diagnostic interview in diverse populations, including adolescence (area under the curve 0.806 to 0.995) (Cairney, Veldhuizen, Wade, Kurdyak, & Streiner, 2007; Cornelius et al., 2013; Furukawa, Kessler, Slade, & Andrews, 2003; Sakurai, Nishi, Kondo, Yanagida, & Kawakami, 2011). The K10 is widely used in general population surveys of health in Canada (Cairney et al., 2007), Australia (Furukawa et al., 2003); Kessler et al., 2002), United States (Kessler et al., 2002), and China (Huang et al., 2009). For descriptive purposes, scores were dichotomized into <20 (likely well) and >/=20 (likely to have an anxiety or depressive disorder). In the main regression analyses, the continuous measure was used (i.e., total summative score)

Socio-demographic covariates.

Biological sex. Biological sex was captured as '0' male or '1' female.

Developmental age. Self reported age was grouped into two categories to reflect different developmental periods including emerging adults (15-24) and young and middle aged adults (25-60). Individuals 60 years of age and older were excluded from the analyses due to low levels of cannabis involvement and lack of power to detect accurate population estimates of effects.

Income. Participants were asked, what is your best estimate of the total household income received by all household members, from all sources, before taxes and deductions, in the past 12 months? This estimate did not include capital gains but included other income sources such as work, investments, pensions or government (i.e. Employment Insurance, Social Assistance, Child Tax Benefit

and other income such as child support, alimony, and rental income). Total household income was captured oridnally but treated continuously with the following response options (in thousands): '1' no income, '2' less than 5, '3' 5-<10, '4' 10 to 15, '5' 15 to <20, '6' 20 to <30, '7' 30 to <40, '8' 40 to <50, '9' 50 to <60, '10' 60 <80, '11' 80+.

Primary role status function. A proxy of SES was captured based on student and employment status. Role status was coded as '0' not working or in school, '1' working or in school part time, or '2' working and/or in school full time.

Table 1
Variable Coding Schemes

Variable/Concept	Coding Scheme
Past Year Substance Use	
Cannabis	Less than once a month or never =0 At least once a month=1
Alcohol Involvement	Past year chronic use 0=no (<12 drinks/week), 1=yes (>/=12 drinks/week) Past year acute use treated continuously (0= never, 1=less than once a month, 2=once a month, 3=2 to 3 times a month, 4=once a week, 5=more than once a week)
Illicit Drug Involvement	Past year use of any illicit substance other than cannabis 0=no, 1=yes.
Current Tobacco Smoking	Categorical variable coded as never (reference group), occasional and regular.
Socio-demographic Characteristics	
Age Group	0=young or middle adult (25-60) 1=emerging adult (15-24)
Sex	0=male 1=female
Income	Total household income treated continuously.
Role Function	Categorical variable coded as not in school or working (reference). Part Time student and/or employment, or Full Time student and/or employment
Year	0=2002 1=2012

Mental Health Outcomes	
Past Year Suicidal Thoughts or Attempts	0=no 1=yes
Past Year MDE	0=no 1=yes
Past month Psychological Distress	Scaled score (Continuous)

Socio-demographic covariates and other non-cannabis substance use are included in this study as potential confounders of the relationship between cannabis and emotional problems. Confounders are variables that are independently associated with both the primary predictor variable of interest and the outcome, sometimes casual agents but not always, but do not lie within the causal pathway (i.e. not a mediator) (Babyak, 2009). The next section discusses the issue of confounding, potential approaches to address confounding and how this study addressed confounding.

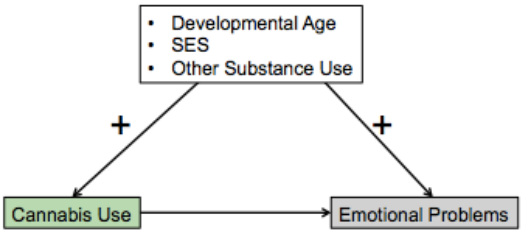
Controlling for Bias

Bias threatens the validity, or credibility, of studies by causing systematic deviations from the true effect (Guyatt, Rennie, Meade, & Cook, 2015). The most pervasive cause of bias is confounding. Confounders influence the association between the predictor and the outcome. Confounders can positively confound, resulting in overestimation of effects when not considered, or negatively confound the relationships, resulting in underestimation of effects (Guyatt et al., 2015). Existing literature on the relationship between cannabis use and emotional problems varies substantially regarding the number and type of confounders adjusted for in analyses. Previous reviews have found studies range from adjusting for no confounders to adjusting for more than 20 potential confounders (Lev-Ran et al., 2014). The confounders most consistently addressed include demographic variables (such as age and gender/sex), SES, other substance use, and other or previous mental illnesses (Kedzior & Laeber, 2014; Lev-Ran et al., 2014; Moore et al., 2007; Twomey, 2017).

Positive confounding occurs when a confounder is positively associated with both the exposure (cannabis) and the outcome (emotional problems) or negatively associated with both (See Figure 2 for positive confounders used in this study). In my thesis, positive confounders related to both cannabis and emotional problems include emerging adulthood, SES, other substance use, and other mental illnesses. Developmental age is a confounder as emerging adults report more cannabis use and more emotional problems than older cohorts (Pearson, Janz, & Ali, 2013b). SES as a potential confounder is discussed in detail

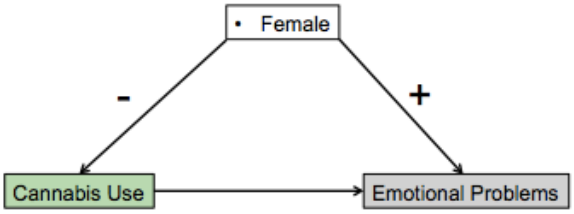
below. Regarding other substance use, many individuals who use cannabis also use other substances (Rotermann & Langlois, 2015); alcohol (Fergusson, Boden, & Horwood, 2011; Kessler et al., 1997, Kushner, et al. 2012), tobacco (Lawrence, Mitrou, Zubrick, 2009), and other illicit substances (Jane-Llopis & Matytsina, 2006; Wong, Zhou, Goebert, & Hishinuma, 2013) have demonstrated independent associations with poor mental health and suicidal behaviours.

Figure 2. Example of positive confounding.



Negative confounding occurs when a confounder is positively associated with the exposure and negatively associated with the outcomes or vice versa (See Figure 3 for negative confounders used in this study). In this study, being a female is a negative confounder as females are less likely to use cannabis compared to males and more likely to experience emotional problems and vice versa for males (Pearson et al., 2013b; Rotermann & Langlois, 2015).

Figure 3. Example of negative confounding.

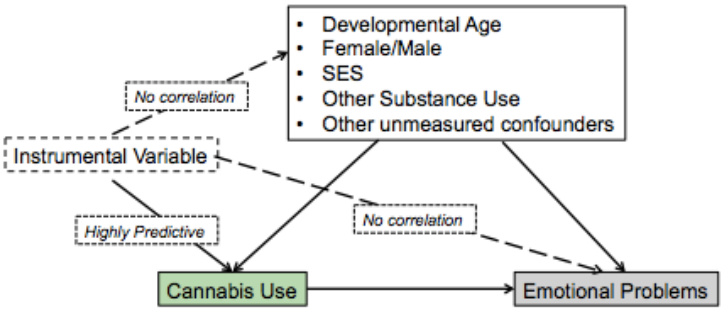


To summarize, this study seeks to account for the most common confounding variables of the association between cannabis use and emotional problems including developmental age, biological sex, other substance use, and SES. Adjusting for these confounders reduces the risk of misattribution and allows for the determination of the association between cannabis and emotional problems over and above other strong correlates. Randomized controlled trials eliminate the risk of confounding by randomly allocating individuals to comparison groups. The goal of randomization is to yield groups balanced on both known and unknown confounding variables (Guyatt et al., 2015). Therefore, in a randomized controlled trial, the difference between the groups can be inferred to

be due to the intervention/treatment. In observational analyses, methods to address confounding can be performed to mimic randomization called pseudo-randomization, such as the use of instrumental variables (Nørgaard, Ehrenstein, & Vandenbroucke, 2017), or through statistical adjustment such as stratification, multivariate models, and propensity scores (Guyatt et al., 2015). Applications of these methodological strategies in the current study are also discussed below.

Instrumental variables. Instrumental variables, rooted in economics, are variables associated with receiving the exposure that are not directly related to the outcome (e.g. the exposure of interest is a complete mediator of the association between the instrumental variable and outcome) and not indirectly related to other predictor or unmeasured confounding variables (See Figure 4) (Lousdal, 2018). By utilizing instrumental variables, one can mimic randomization, and control for known and unknown confounders. Using instrumental variables requires a two step analysis whereby regression is used to predict the association between the instrumental variable and the exposure of interest and then the instrumental variables is used as the independent variable for predicting the outcome of interest (Lousdal, 2018). However, determining appropriate instrumental variables is often difficult (Nørgaard et al., 2017). Examples of instrumental variables include random allocation, proximity, calendar time, provider or organizational preference, or genetics. There is a lot of unmeasured confounding in the current study (i.e. strain of cannabis, potency, method of delivery, tobacco use, combined used). However, there are no potential instrumental variables for cannabis use in the CCHS-MH– i.e. a variable that influences ones decision to use cannabis of a certain frequency but unrelated to confounders or emotional problems. Therefore, this study does not use instrumental variables to account for bias.

Figure 4. Example of an instrumental variable.



Stratification. Stratification is used to 'fix' the level of confounding, i.e. remove confounding by eliminating variation within the confounding variable in the analysis (Pourhoseingholi, Baghestani, & Vahedi, 2012). Analyses are done separately for each strata and then effect sizes between models are compared using the Mantel-Haenszel estimation. Mantel-Haenszel estimation determines an adjusted result according to the strata. If a difference exists between the crude and the adjusted results, confounding is present. If the crude result does not differ from the adjusted, analyses can be combined as confounding is unlikely (Pourhoseingholi et al., 2012). Stratification is most helpful when the confounder of interest has few strata (e.g. gender/sex) and there are few confounding variables of interest. This study could have stratified based on developmental age (binary) and/or biological sex (binary), but since there were multiple other confounders of interest, stratification was not used.

Propensity scores. A propensity score is the conditional probability of an individual being exposed/treated given certain covariates (Rosenbaum & Rubin, 1983). A common way to estimate the propensity score in observational studies is through conducting a logistic regression, where treatment or exposure status (predictor) is regressed on other confounding or baseline characteristics. The probability of being in the exposure or treatment group becomes an individual participants propensity score (Austin, 2011). This score can be used for matching, stratification, inverse probability of treatment weighting (IPTW), and multivariate adjustment using the propensity score. Propensity scores are most useful when the model needs to be adjusted for a large number of confounders and the individual effects of each confounder are not of interest. In this study, propensity scores were not used primarily because the sample was large yielding appropriate power to adjust for all confounder of interest independently and a stepped approach was used to see the influence of certain types of confounders (as opposed to simultaneously adjusting for all confounders).

Multilvariate models. Multivariate analyses are commonly used in social and biomedical literature to control for confounding, as many covariates can be controlled for simultaneously (Pourhoseingholi et al., 2012). By having multiple variables simultaneously in a model, the effect sizes reflect unique effects on the outcome or their incremental validity of predicting the outcome over and above other factors in the model. When using this approach, it is imperative that important predictor variables and confounders were measured in a way that is valid and reliable (Guyatt et al., 2015). In this study, a multivariate model approach was used to address the issue of confounding. Additionally, a stepped analyses was performed to determine the magnitude of influence of confounders on the association between cannabis use and emotional problems.

This study. In conclusion, multiple methods of addressing confounding in observational studies were considered for this study. There were no plausible instrumental variables available for inclusion in this analysis. Future studies may consider using proximity to dispensaries or number of visits to dispensaries as potential instrumental variables. There were too many confounders of interest to employ stratification and too few to merit propensity score matching. Future studies may consider these approaches depending on number of confounders of interest and whether they are interested in a stepped or concurrent approach. In this study, due to the number of confounding variables of interest and large sample size, a multivariate analysis was used to control for confounding variables and stepped approach to demonstrate the magnitude of the confounding influence.

SES Confounding Issue: Emerging Adulthood and SES

My thesis examines the association between cannabis use and emotional concerns including MDEs, suicidal thoughts and attempts, and psychological distress. As previously stated, research on the association between cannabis and emotional problems commonly adjust for the potential confounding influence of SES. Although commonly addressed, how SES is measured is inconsistent across studies and becomes problematic when attempting to measure across the lifespan. Given one of my primary covariates and potential moderators of my main objective is developmental age, a valid and reliable measure of SES across the lifespan is required to accurately account for the influence of SES.

Previous studies have found an inverse association between SES and depression in adults (Everson, Maty, Lynch, & Kaplan, 2002; Holzer et al., 1986; Lorant et al., 2003; Muntaner, Eaton, Diala, Kessler, & Sorlie, 1998), mood and anxiety disorders in older adolescents and adults (Muntaner et al., 1998), and mental disorders among children and adolescents (Reiss, 2013). There also appears to be an association between SES and cannabis use, although this association seems to be more complicated. For example, there is evidence suggesting a positive association between childhood SES and cannabis use during emerging adulthood (Patrick, Wightman, Schoeni, & Schulenberg, 2012) but other evidence to suggest that although adolescents from families with higher SES are more prone to experimenting with cannabis, adolescents from families of lower SES are more likely to engage in frequent, intensive, and hazardous use (Legleye, Beck, Khlat, Peretti-Watel, & Chau, 2012). Overall, SES is an important covariate to consider when quantifying the association between cannabis use and mental health outcomes, particularly among adolescents and emerging adults.

Emerging adulthood is a distinct developmental period characterized by instability, identity explorations, feeling in-between, and optimism, often referred to as extended adolescence (Arnett, 2000, 2015). The creation of this new developmental stage - emerging adulthood - has developed in response to societal shifts including the prolongation of education past high school and increases in post-secondary school enrolment (for both men and women), steep increases in the average age of marriage and parenthood, increasing job insecurity, and decreases in the perceived value of becoming an adult (Arnett, 2000, 2015). This has created a period of time straddling adolescence and adulthood in which an individual is independent of parents, but not yet an economically, self-sufficient stable adult.

The developmental period of particular interest in this study is emerging adulthood. Typically emerging adulthood is operationalized as individuals between 18 to 25 years (Arnett, 2000, 2015) but in this study emerging adulthood is operationalized as 15 to 24 years. This combination of late adolescence and "true" emerging adulthood was intentional to capture a period of neuronal developmental vulnerability. The brain continues to develop until about 25 years of age and cannabis has been shown to act on the part of the brain that is critically involved in neuronal maturation (the ECS) (Arain et al., 2013; Dow-Edwards & Silva, 2017; Gavin et al., 2009). The analyses compare "emerging adults" aged 15 to 24 years, or those that may experience neurodevelopmental vulnerability to the effects of cannabis, to "young and middle aged adults" aged 25 to 60 years of age, whose brains are fully developed. However, this moderating factor becomes problematic when attempting to adjust for SES.

Measuring SES among Emerging Adults. Reiss (2013) found that child and adolescent SES is most commonly measured through: (a) household income; (b) parental education level; and (c) parental occupation status or an index combining these variables. Other common indicators include (d) relative poverty measured through an income below a certain level and/or receipt of welfare benefits; and (e) scales of family assets or affluence. Importantly, parents commonly provide indicators of SES for children and adolescents. When adolescents self report SES (15 years of age and older), different measures of SES are used, often ones that assess perceptions of financial difficulties, social position in comparison to peer group and/or an index of material assets in the family. Even within specific variables, wording and response options are inconsistent and not directly comparable between studies. Measures of SES in the general population, not considering developmental age, are similarly variable and have previously been criticized as lacking consistency, reliability, and validity (Shavers, 2007).

Approaches to measuring SES may be even more complex for emerging adulthood. First, family income or parental education may not be relevant indicators of emerging adults' SES as this is a period of time where individuals may not live at home with their parents nor receive financial support from them. Secondly, emerging adulthood is a period of transition between school and professional career, where individuals are typically: continuing their education with or without financial assistance, in an unpaid or low paying internship, and/or working part time, minimum wage, or entry level job(s). With this in mind, employment status or current income are not appropriate indicators of an individual's underlying capabilities during this developmental period. Additionally, using postal codes to capture neighbourhood income is also problematic, since residential mobility is high during this period of development and emerging adults may be living in residence or directly around post-secondary school campuses in "student housing." Emerging adults may also be living with students; so reported household income may be an inadequate index of availability of material resources from their families. Lastly, capturing total expenses (i.e. housing, schooling, food, leisure, etc.) and total income (i.e. jobs, parental support, external financial support such as scholarships and loans) may also not be accurate representations of SES, particularly if an individual is continuing their education. For example – an individual who is attending medical school has high living and school expenses, little to no time for work, and may not be receiving any financial support from parents or external sources. Would one then consider this medical student of low SES, despite prospects for high SES in the future?

Exploring the use of Subjective Financial Situation. A recent study by Williams et al. (2017) suggested the use of subjective financial situation (SFS) to measure SES among emerging adults, acknowledging that childhood financial status and parental education would not accurately represent current SES in the moment of transition from adolescence to adulthood. Emerging adult SFS was measured with the item, "*Considering your own income and the income from any other people who help you, how would you describe your overall personal financial situation*?" Response options include: live comfortably, meet needs with a little left, just meet basic expenses, and don't meet basic expenses.

This study used nationally representative data from the United States (US), from the Truth Initiative Young Adult Cohort, looking specifically at the subsamples of 18-24 and 25-30 year olds (n=2182) to assess the validity of this SFS item (Williams et al., 2017). They compared their SFS measure to conventional SES measures including parental and personal educational attainment and total household income. They also compared the SFS measure for

emerging adults to a previously validated childhood SFS item, "*Think about your family when you were growing up, from birth to age 16. Would you say your family during that time was pretty well off financially, about average, or poor?*" with response options including: pretty well off financially, about average, poor, and it varied.

They found significant differences between the 18-24 and 25-30 year old samples on all SES measures, except respondent education. Significant, although weak, correlations were found between SFS and other SES variables demonstrating convergent validity, although the magnitude of these correlations differed based on age group. For example, SFS and household income were positively correlated in both age groups, however it was more strongly correlated in the older sample (r=0.40), compared to the younger sample (r=0.25). It is difficult to evaluate the convergent validity of the SFS measure against existing measures, as the point of utilizing a different approach such as the SFS is to address measurement concerns of existing measures. Therefore, weak correlations do not necessarily negate the utility of this measure.

This study also evaluated the predictive ability of SFS, acknowledging that low SES is consistently associated with poorer health outcomes (Williams et al., 2017). They found higher SFS to be significantly related to better quality of life and higher subjective health status across both age groups in a dose-response fashion. Subjective childhood financial situation and highest parental education level were not significantly related to any health outcome in either age sample. Importantly, household income and respondent education, two of the most common measures of SES in adults, were significantly related to health status and Body Mass Index in the older sample but **not** in the younger (i.e. emerging adult) sample. This provides evidence to support the notion that the age group of "young adults," previously defined as 18-30 years of age, needs to be further broken down to capture emerging adulthood. Furthermore, these differences in the predictive ability of SES measures support the need to re-operationalize SES among emerging adults.

It is important to note this is a single study only evaluating the predictive ability of the SFS measure on three health outcomes (Williams et al., 2017). It is also important to acknowledge this measure was created for and tested on individuals in the US. Further testing of this measure, or measures like the SFS described by Williams et al. (2017), is justified in different countries, for different health outcomes, and in different age groups. Future research should also evaluate the impact of negative cognitive bias, which is the selective paying attention

negative aspects of experiences and interpretations associated with mood and anxiety disorders, on accurate measurement of SFS (Beck, 2008).

Although SFS presents a potentially valid and reliable measure of SES across the lifespan, there was no measure of SFS in the CCHS-MH. Therefore, this approach could not be used in the current study.

Exploring the use of Subjective Social Status. In this study, I needed a measure that not only addressesed SES among emerging adults, but a measure that accurately assessed SES across the lifespan. Several studies have explored the psychometric properties and predictive ability of subjective measure of social status based on a metaphorical ladder of social status, where participants are asked to rank themselves/family relative to other people/families in their respective country. i.e. "*At the top of the ladder are the people who are the best off – they have the most money, the highest amount of schooling and the jobs that bring the most respect. At the bottom of the ladder are the people who are the worst off – they have the least money, little or no education, no job or jobs that no one wants or respects*." This tool, or something similar, has been explored in adults (Adler, Epel, Castellazzo, & Ickovics, 2000; Operario, Adler, & Williams, 2004; Singh-Manoux, Marmot, & Adler, 2005), youth (Goodman et al., 2001; Goodman, Huang, Schafer-Kalkhoff, & Adler, 2007; Karvonen & Rahkonen, 2011), and emerging adults (Finch, Ramo, Delucchi, Liu, & Prochaska, 2013) demonstrating convergent validity (i.e. significant, although weak, correlations with other SES indicators) and predictive ability of various health outcomes. This approach, or something similar, may be worth exploring for the purpose of adjusting for SES across the lifespan.

Similar to SFS, subjective social status presents another potentially valid a reliable measure of SES across the lifespan. Again, there was no measure of subjective social status in the CCHS-MH. Therefore, this approach could not be used in the current study.

SES in the CCHS-MH. SES indicators in the CCHS-MH include: personal income, total household income, employment and student status, personal and household member educational attainment, and immigrant status. In this study, I was interested in adjusting for SES among adolescents and emerging adults (aged 15-24 years) and young and middle aged adults (aged 25-60 years).

One of the most commonly used indicators of SES is total household income. I explored the distribution of total household income across three developmental stages: late adolescence (15-17), emerging adulthood (18-24),

young and middle aged adulthood (25-60). I further separated late adolescence from my broader categorization of emerging adulthood, as 96% of secondary students in Canada live at home (i.e. total household income may be more applicable) (King & Hoessler) compared to 60% of 20-24 year olds (Statistics Canada, 2012). It is important to note that in the CCHS, total household income is assessed through questions asked of the respondent. Therefore, in the CCHS-MH if the youth is the selected respondent in the household, he/she will be the source of income information. As depicted in Figure 5, adolescents and emerging adults had a higher proportion of missing responses than young and middle aged adults indicating that younger individuals are having a more difficult time answering this question. In comparison to other age groups, a larger proportion of emerging adults reported low total household income (i.e. less than $40,000) compared to other developmental periods.

I also explored correlates of SES across the two age groups. As shown in Table 2, using the Phi coefficient (φ) for correlations between binary variables and Point Biserial (r_{pb}) correlations between binary and continuous variables, total household income, marital status, education, student status, and employment were all significantly, but weakly, associated with one another in both age groups. However, conventional correlates (total household income, education, employment) were more strongly correlated in the young and middle-aged adult sample, compared to emerging adults.

Figure 5. Total household income across developmental stages.

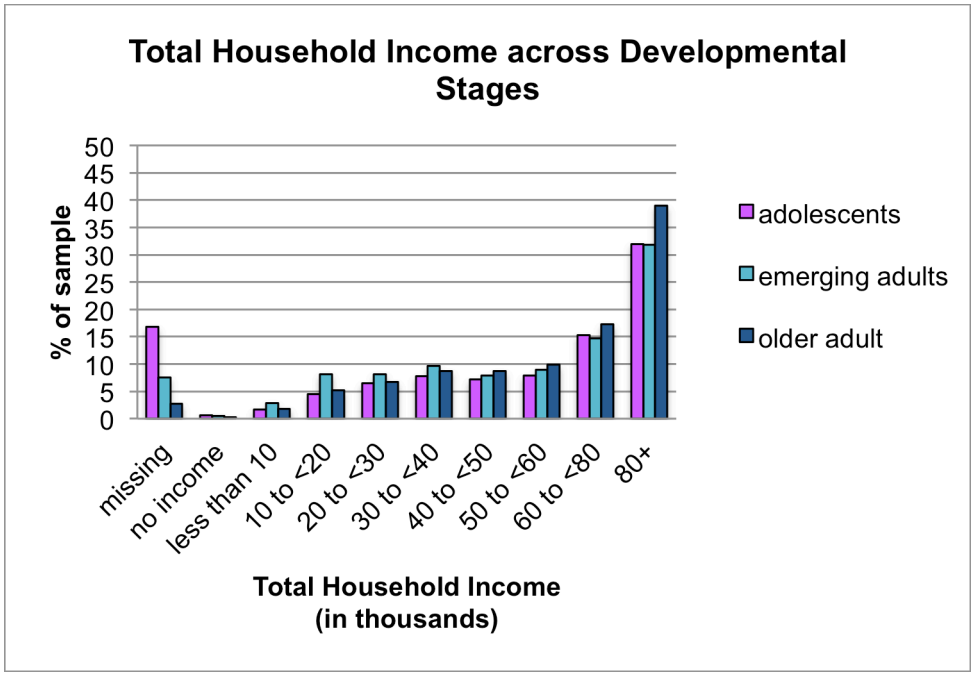


Table 2

SES Correlates

	Total household Income		Marital Status		Education		Student Status		Employment	
	E	A	E	A	E	A	E	A	E	A
Total household Income	1	1								
Marital Status	**-0.13**	**0.33**	1	1						
Education	**0.03**	**0.23**	**0.15**	**0.02**	1	1				
Student Status	**0.06**	**-0.08**	**-0.27**	**-0.08**	**-0.18**	**0.10**	1	1		
Employment	**0.13**	**0.29**	**0.13**	**0.03**	**0.16**	**0.07**	**-0.25**	**-0.08**	1	1

Notes. E=Emerging Adults (15-24), A=Young and Middle aged Adults (25-60); **Bold** = statistically significant at $p<0.05$

What do we do? It is important to revisit the underlying reason for controlling for SES in this research study. As previously discussed, SES may be a confounder in the association between cannabis use and mental health outcomes (i.e. low SES individuals are more likely to use cannabis and also more likely to experience mental health difficulties). Not controlling for SES may lead to spurious associations between cannabis and mental health, resulting in incorrect inferences that cannabis is related to mental health when the association is actually due to SES. Existing literature (Legleye et al., 2012; Patrick et al., 2012) appears to focus on the association between family SES during childhood and adolescence as predictors or risk factors of the development of mental health concerns and the use of substances. Therefore, for this study, I was most interested in the SES of a participant's family growing up. However, there is no measure of family SES during childhood and adolescence (unless currently an adolescent) in the CCHS-MH. Also, family SES during childhood and adolescence may be a relevant covariate for emerging adults, but does it remain relevant for the comparison group of older adults?

Using measures available in the CCHS-MH, I attempted to use role function as a proxy of SES across the lifespan. This variable was a combination of student and employment status, capturing individuals that are not working nor in school), working or in school part time (part-time), and working and/or in school

full time (full-time). Revisiting correlations identified in Table 2, it is shown that employment is one of the strongest correlates of income across both developmental periods, although it is weakly correlated (emerging adults r=0.13; young and middle aged adults r=0.29) while student status is one of the weakest correlates (emerging adult r=0.06; young and middle aged adults r=-0.08). Although weak correlations between role function and income were found, as stated by Williams et al. (2017), correlations with income and other SES indicators may not be appropriate for testing convergent validity of new measures because the current measures are not adequately capturing the variable of interest.

Overall, there is no agreed upon measure of SES in the CCHS-MH component for emerging adults. For the purpose of my study, I adjusted for total household income and role function in sensitivity analyses, but did not include these variables in the primary analyses.

Data Analysis

All data analyses were performed at the McMaster Research Data Centre using SPSS 25 and SAS 9.4.

Missingness. Missingness can be present in either total non-response or item non-response. Total non-response is accounted for in the weighting procedures described below. The use of face to face or phone interviews should have limited item non-response. This being said, I examined frequencies, patterns, and types of missing items through Missing Value Analyses in SPSS. Analyses of missing items were done for main variables including: cannabis use, suicide, MDE, psychological distress, biological sex, developmental age, alcohol use, and other illicit substance use. Data were considered MCAR (missing completely at random) if Little's MCAR test, a Chi-Square test for missing completely at random, was not significant (Tabachnick & Fiedell, 2013). Missingness was deemed not MCAR, so cases were dummy coded where a complete case was coded '0' and an incomplete case was coded '1' and this dummy variable was regressed individually on each variable in the model to determine if model variables are meaningfully related to missingness (i.e. missing at random).

When item non-response presented a large or systematic problem, Statistics Canada statisticians conducted advanced imputation procedures to account for missingness (Statistics Canada, 2003, 2013). There were technical problems in the skip pattern of the 2002 suicide module, where some individuals were not asked questions regarding suicidal thoughts and attempts in the past 12 months (Statistics Canada, 2003, 2013). Statistics Canada was able to use

deterministic imputation for all missing suicide attempts and ¼ of missing suicidal thoughts. The remainder of the missing responses were determined utilizing logistic regression imputation (Statistics Canada, 2003, 2013). In 2012, missing household income values due to response refusal or lack of knowledge were also imputed (and flagged) (Statistics Canada, 2003, 2013). Most other items had limited missing responses.

Variable missingness ranged from 0% (developmental age, biological sex, and year) to 1.4% (cannabis use) for main variables of interest for the total sample (See Table 3). 97.5% of the sample has complete responses for main variables including: cannabis use, suicide, MDE, psychological distress, biological sex, developmental age, alcohol use, and other illicit substance use. Of the 2.5% missing, almost half of the missing cases were only missing one variable (See Table 4). The most common missing data patterns include only missing responses for: (a) cannabis (1.08% total sample), (b) MDE (0.31% of total sample), and (c) K10 scores (0.31%). The proportion missing for particular variables, proportion of total missing, and patterns of missing were similar at both time points. A binary variable was created to classify missing versus complete cases. This variable was used to assess bivariate associations between missingness and independent and dependent variables in the proposed model. These bivariate logistic regression analyses revealed that acute alcohol use (binge drinking), other illicit drug use, experiencing suicidal thoughts or endorsing attempts, experiencing MDE, endorsing higher psychological distress and being a male or an emerging adult was positively related to missingness while income is inversely related (See Table 5). Since missingness was minimal and the most common missing variable is the primary predictor (cannabis), the following analyses were performed on complete cases (observed n= 43,466; 97.5% of full sample). Items used in sensitivity analyses, including functional status; total household income, and cigarette smoking were not used for the creation of the sample of complete cases. Therefore, there were some additional missing cases in samples for the sensitivity analyses (observed n= 41,180 for sensitivity analysis adjusting for total household income; observed n= 43,105 for sensitivity analysis adjusting for function; observed n=16772, for sensitivity analyses adjusting for cigarette smoking in 2012 sample only).

Table 3
Percent Missing for Each Variable

Variable	% missing
K10 Psychological Distress Score	0.4
Suicidal Thoughts and/or attempt	0.1
MDE	0.4
Emerging Adulthood	0.0
Biological Sex	0.0
Year	0.0
Cannabis Use	1.4
Chronic Alcohol Use	0.2
Other Illicit Drug Use	0.4
Acute (Binge) Alcohol Use	0.4

Table 4
Number of Missing Items for Missing Cases

# items missing	Percent
0	97.5
1	1.2
2	0.5
3	0.5
4	0.1
5	0.2
6	0.03
7+	0.01

Table 5

Univariate Logistic Regression Predicting Missingness[1]

Effect	OR	95% Confidence Limits		p-value
Year	1.136	0.941	1.371	0.1847
Emerging Adult	2.141	1.787	2.564	<.0001
Female Biological Sex	0.795	0.66	0.959	0.0163
Psychological Distress	1.046	1.03	1.062	<0.001
MDE	1.845	1.241	2.744	0.0026
Suicidal Thoughts or Attempts	1.728	1.177	2.537	<.0001
Cannabis Use at least once per month	1.164	0.686	1.976	0.5727
Acute (Binge) Alcohol Use	1.101	1.024	1.184	0.0099
Chronic Alcohol Use	0.972	0.719	1.315	0.8558
Other Illicit Drug Use	1.981	1.337	2.936	0.0007
Total Household Income	0.909	0.871	0.947	<.0001

Analysis Plan. I first explored data descriptively by looking at the mean, standard deviation (SD), frequency counts, minimums and maximums for each variable. Correlational matrices are also presented, using Phi (φ) for correlations between binary variables and Point Biserial (r_{pb}) correlations between binary and continuous variables. Low, moderate, and high degree correlations were operationalized as <0.3, 0.3 to <0.5, and >=0.5 respectively (Tabachnick & Fiedell, 2013).

I performed stepped analyses using linear regression for psychological distress and binary logistic modelling for MDE and suicidal thoughts and behaviours. Time was accounted for in the regression analysis by including a binary indicator for time (2002 vs 2012) and an interaction term between cannabis use and time. This allowed us to determine (a) if there have been temporal shifts in the mental health outcomes; and (b) if the associations between cannabis and mental health related outcomes have become stronger or weaker across time. This approach consisted of four overarching steps:

Step 1. Step 1 was comprised of a set of exploratory analyses to provide empirical rationale for categorizing cannabis frequency in primary analyses. I

[1] Weighted and bootstrapped for population based estimates

first looked at distributions of cannabis use across developmental periods to ensure relevance of frequency categories. Next I performed regression analyses exploring the effect estimates of frequency of cannabis use and mental health. Based on these results, I collapsed cannabis frequency categories appropriately. (i.e. if frequency categories yield similar effect estimates that are consistent across age groups, I collapsed into one category).

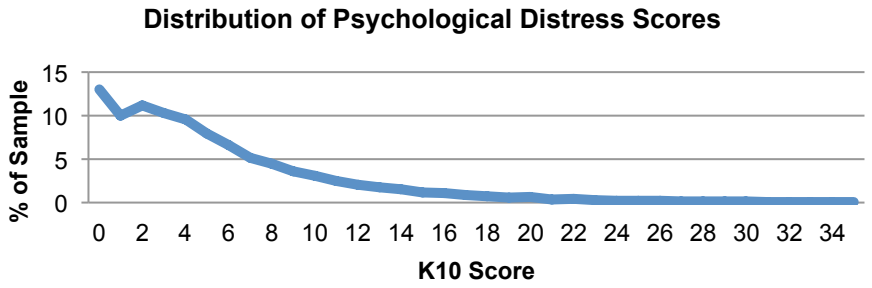
Step 2. In Step 2, I used collapsed cannabis response categories to determine the associations between cannabis frequency (model 1), time, and mental health outcomes controlling for developmental age and biological sex. Three sets of interaction terms were examined:

1. Cannabis use by time (model 2)
2. Emerging adulthood by cannabis use by time (with lower order interactions) (model 2A)
3. Female sex by cannabis use by time (with lower order interactions) (model 2B)

No three-way interactions terms were significant ($p>0.05$) and therefore these higher order, and the associated lower order, interactions were not retained in subsequent models.

Model fit. Since psychological distress was positively skewed in the population (See Figure 6), model fit was tested for psychological distress regressed on (a) biological sex, year, and monthly cannabis frequency (basic); and (b) the basic model in addition to the year by monthly cannabis use interaction term (primary model). Several linear and generalized linear models were examined including: normal distribution with raw K10 scores, gamma distribution with an identity link, gamma distribution with a logit link, exponential distribution with an identity link, exponential distribution with a logit link, and normal distribution with log transformed K10 scores. Model fit was evaluated and compared using Akaike's Information Criterion (AIC) and Bayesian Information Criterion (BIC) (Tabachnick & Fiedell, 2013). These statistics consider the likelihood (L) for a model with k parameters and n observations, where lower values reflect better fit. Both statistical tests consider complexity (i.e. number of parameters and sample size) where AIC is calculated -2InL+2k and BIC is calculated -2lnL+kln(n) (Tabachnick & Fiedell, 2013).

Figure 6. Distribution of psychological distress (K10) scores.



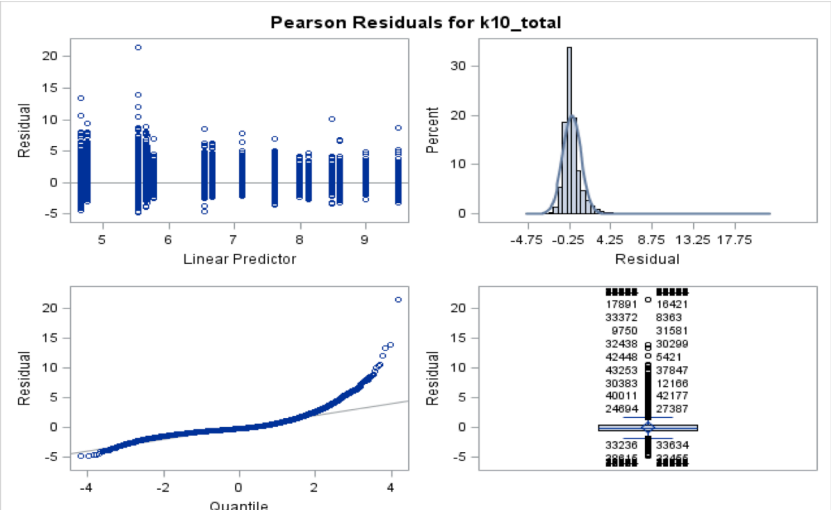
Results of model fit tests are presented in Table 6. These statistical tests demonstrate that the best fit is produced by a Generalized Linear Model (GLM) with a gamma distribution and identity link followed by a normal Gaussian linear model using raw psychological distress scores. Since GLM does not provide the capability of bootstrapping, the following analyses were performed assuming a normal distribution using non-transformed K10 scores (also the most clinically applicable). As seen in Figure 7, model fit remains poor due to evidence of heteroscedasticity and non-normality. Linear regression has demonstrated robustness even with deviations in the normality assumptions, especially in large datasets (Schmidt & Finan, 2017). However, heteroscedasticity, regardless of the size of the dataset, is influential (Schmidt & Finan, 2017). Despite evidence of non-normality and heteroscedasticity, the large sample size, bootstrapping, and search for relatively small effects with small standard errors provides confidence in the findings for psychological distress.

Table 6

Model Fit Tests for Linear Regression Predicting Psychological Distress

Model fit	Gaussian, identity raw K10	Gamma, identity	Gamma, logit	Exponential, identity	Exponential, logit	Gaussian, identity logK10
Basic Model						
AIC	291225.3	237506.8	365480.6	1.079E+24	1.08E+24	315503.5
BIC	291277.3	237558.1	365531.9	1.079E+24	1.08E+24	315555.6
Primary Model						
AIC	291218.9	237503.8	365482.6	1.08E+24	1.08E+24	315506.4
BIC	291279.7	237563.6	365542.4	1.08E+24	1.08E+24	315567.2

Figure 7. Model fit tests for the primary model assuming a Gaussian distribution and identity link on non-transformed psychological distress scores.



Step 3. It is important to control for the effects of comorbid substance use to determine the unique effect of cannabis use over and above other substance use on mental health outcomes. I present both unadjusted (Step 2) and adjusted (Step 3) models to provide readers with both liberal and conservative estimates of effects. In Step 3 (model 3), alcohol (binge and chronic use) and illicit drug use covariates were added to the final model from Step 2 (i.e. developmental age, year, biological sex, cannabis use, and cannabis use-by-time interaction).

Sensitivity analyses. Lastly, I performed three sensitivity analyses to examine the extent to which the following additional variable impact the observed associations between cannabis use and mental health outcomes: (a) smoking frequency (using data only from 2012), (b) total household income (model 4A), and (c) functional status (SES proxy) (model 4B). These variables were used in sensitivity analyses as opposed to primary analyses due to measurement limitations and concerns previously discussed.

Commonality analysis. To quantify the shared variance of substance use variables on the outcome, I performed a commonality analysis to determine the unique and shared effects of cannabis, binge drinking, chronic drinking, and other drug use on the outcomes of interest. See Figure 8 for Analytic Guide and Table 7 for Equations.

Figure 8. Commonality analysis analytic guide.

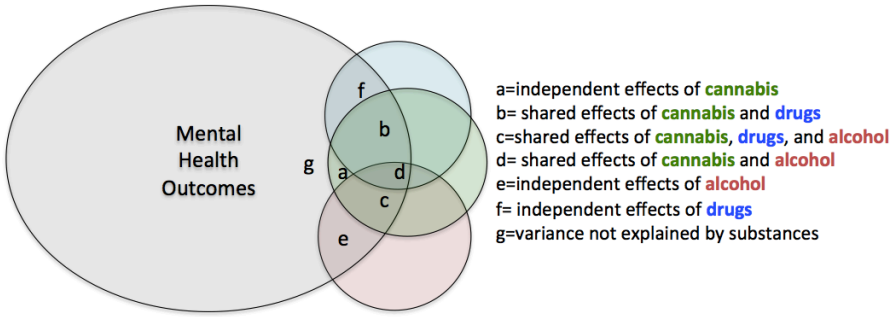


Table 7

Commonality Analysis Equations

	Effects	Equations
Unique	Cannabis	R^2(Can Alc Drug)-R^2(Alc Drug)
	Alcohol	R^2(Can Alc Drug)-R^2(Can Drug)
	Other Drugs	R^2(Can Alc Drug)-R^2(Can Alc)
Common	Cannabis Alcohol	R^2(Can Drug)+ R^2(Alc Drug)-R^2(Drug)-R^2(Can Alc Drug)
	Cannabis Other Drugs	R^2(Can Alc)+ R^2(Drug Alc)-R^2(Alc)-R^2(Can Alc Drug)
	Drugs Alcohol	R^2(Drug Can)+ R^2(Alc Can)-R^2(Can)-R^2(Can Alc Drug)
	Cannabis Alcohol Other Drugs	R^2(Can Alc Drug) - R^2(Can)+R^2(Alc)+R^2(Drug)- R^2(Can Alc)+R^2(Can Drug)+R^2(Alc Drug)

Description of Statistical Modelling Assumptions & Testing.

All of following statistical approaches and equations are taken from Tabachnik and Fidell (2013) and Hosmer, Lemeshow, & Sturdivant (2013).

Linear Models

$$Y = \beta o + \beta_1 x_1 + \beta_2 x_2 + \cdots + \beta_k x_k$$

Assumptions. The assumptions for linear regression include: *existence, linearity, independence, absence of multicollinearity, normality, and homoscedasticity*. *Existence* is implied by the scan of the literature. The data were collected in a way for us to be able to infer *independence.* I diagnosed *multicollinearity* by obtaining Variance Inflation Factor (VIF) statistics. If VIF was >10 or if the standard errors increased by two times or more, I planned to combine or drop variables from the final analyses. I assessed *normality, linearity, and homoscedasticity* by examining residual scatterplots (one axis is predicted scores and the other is error of prediction). Transformations or GLM were tested for model fit, as assumptions were not met.

Outcomes. Beta coefficients, 95% Confidence Intervals (CI), and T-tests were used to test the statistical significance of independent variables. Interaction effect sizes were calculated through adding the cannabis beta coefficient to the year by cannabis interaction beta coefficient. The associated standard errors (SEs) were calculated by taking the square root of the sum of the variance (Var) for cannabis, variance for the interaction, a two times the covariance between cannabis and the interaction. The SE was then used to calculate the lower and upper bunds of the interaction CI. See the following for calculations:

$\beta_{\text{Interaction}} = \beta_{\text{cannabis}} + \beta_{\text{year*MJ}}$
$\text{Variance} = \text{Var}_{\text{cannabis}} + \text{Var}_{\text{year*MJ}} + 2\text{Cov}_{(\text{year*MJ, cannabis})}$
$\text{Standard Error} = \sqrt{Var}$
Confidence Interval = new effect size +/- (1.96*new Standard Error)

The use of a large data set poses the threat of revealing small statistically significant effects sizes. When interpreting results, clinically meaningful effect sizes and CI beyond statistically significant effects were considered. In linear models, meaningful results were defined as a 2.5-point change (half a category) in psychological distress when interpreting beta-coefficients (Andrews & Slade, 2001).

Binary Logistic Models.

$$\text{In}[\text{pr}(\text{Y} = 1)] = \beta o + \beta_1 x_1 + \beta_2 x_2 + \cdots + \beta_k x_k$$

Assumptions. The assumptions for binary logistic regression include: *existence, linearity of the logit, independence, and absence of multicollinearity*. I assessed *existence, independence,* and *absence of multicollinearity* through the same procedures as linear regression. I tested *linearity of the logit* through the Box-Tidwell test, where terms composed of interactions between each predictor and its' natural log are added to the logistic regression model. If one or more of the added interaction terms are statistically significant, the assumption is violated. I planned to perform transformations or different link functions in GLM if linearity assumption was not met, but this was not required.

Outcomes. Odds Ratios ($OR = e^{B_j}$), 95% CIs, and Wald Tests ($p<0.05$) are used to test the statistical significance and clinical importance of each independent variable. The interaction effect size and confidence interval were calculated similarly to linear models using the Ln (odds) or the non-exponentiated beta coefficients. For logistic models, all outcomes are additionally exponentitated after calculations are completed to obtain the OR and CI for the interaction. In logistic models, a clinically meaningful result suggests beta-coefficients of at least ~0.37 ($P<0.05$), which is equivalent to a small effect size according to Cohen of ~0.2 (Cohen, 1988). This would translate to an OR of ~1.45 which is similar to previous meta-analyses of cannabis use and mental health outcomes which used OR 1.5 as the cut-off for clinically meaningful effects (Kedzior & Laeber, 2014; Twomey, 2017).

Application of Weights and Bootstrapping.

Weighting. Statistics Canada has provided weights for both the CCHS-MH datasets in 2002 and 2012 to ensure national representation of the responses (Statistics Canada, 2003, 2013). In order to make inferences about the Canadian population, each respondent receives a survey weight that corresponds with the number of people in the Canadian population they represent. These weights are used in the analysis to be considered representative of the Canadian population. A description of the derivation of the weights in 2002 and 2012 is presented below.

Summary: 2002 weighting strategy (Statistics Canada, 2003). The first step used a weight provided by the LFS, which served as the sampling frame, to determine the probability of selecting a particular dwelling in a stratum (each province is broken down into strata determined by urbanicity or rurality, SES, and

geography), adjusting for differences in the number of dwellings selected per stratum in the CCHS-MH 2002 compared to the LFS. The weight was then stabilized due to oversampling in some areas. The next step removed out of scope units, such dwellings that are under construction, vacant, seasonal, or secondary homes. The weights of non-responding households were redistributed to responding households using propensity classes formed from logistic regression models that used the evidence of the non-responders that was known (e.g. geography, time of sample). Household-level weights were then converted to individual-level weights. This was done by multiplying the household weight by the probability of a specific person being selected based on the ages of individuals in the household. Prior to determining the sampled individual in a household, a roster of people living within the household is created. If the selected individual did not respond, similar methods as household non-response were used for individual nonresponse but with more data regarding characteristics of household members (due to the initial creation of the roster). Finally, **post-stratification** was done to ensure final weights corresponded with population estimates in the provincial and regional levels for province by age and biological sex groups. The final weighting variable (WTSB_M) was used for all analyses after cleaning and screening the data.

Summary: 2012 weighting strategy (Statistics Canada, 2013). Similar steps were done to calculate weights in 2012. The first step in 2012 also used the weight provided by the LFS, adjusting for differences in the number of clusters and subsampling strategies used in the CCHS-MH 2012. The next steps were the same in removing out of scope units, accounting for household nonresponse (additionally used number and time of attempted contacts), converting to individual level weights, and adjusting for individual level nonresponse. Instead of the post-stratification used in 2002, 2012 used **winsorization** and **calibration**. Winsorization trimming was a strategy used to adjust outlying weights when an individual respondent represents a very large proportion of their province by age by biological sex domain. Lastly, **calibration** ensured equal responses in each season of sampling (to avoid a seasonal effect) and ensure the sum of weights correspond to population estimates at the provincial level (Statistics Canada, 2013). The final weighting variable (**WTS_M**) was used for all analyses after cleaning and screening the data.

Bootstrapping. Due to the complexity of the sampling and weighting in the CCHS-MH, particularly the clustered data, resampling methods must be employed to estimate the precision of effect estimates. This occurs by sampling and replacing the primary sampling units (the sample for which I have observable data) within each stratum (province by age by biological sex) to adjust weights to

reflect the full sample (Canadian population). Both the 2002 and 2012 user guides suggest using bootstrapping methods and 500 bootstrapping re-sampling weights are provided for all observations. Weights of '0' were replaced with '0.000000000001' as weights cannot be 0 in SAS.

Multiple testing. To account for multiple testing and an inflated risk of obtaining a false positive result (type 1 error), I adjusted for the false discovery rate (FDR), or the proportion of significant results that are actually false. I used the approach developed by Benjamin and Hochberg (1995). This involves:

1. Ordering p values from smallest to largest
2. Ranking each p value (k=1 is the smallest, k=2 is the second smallest, etc.), from 1 to m, where m is the total number of tests (m=5 in the primary analysis with the time by year interaction term)
3. Each test then gets its' own critical value, which is calculated as alpha*(k/m)
4. Identifying the largest p-value that is smaller than its' critical value, and reject that test along with all the tests that have a higher rank.

The new 'p-value' then becomes the p-value that is associated with the Benjamin-Hochberg critical value of <0.05.

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Results

This chapter presents the results for the secondary analysis of the CCHS-MH 2002 and 2012 described in Chapter Two. The following section will describe the sample and present the results for step-wise models that test the interaction between monthly cannabis use and time on emotional problems, sensitivity analyses, and the commonality analysis outlined in Chapter Two.

Descriptive Statistics

Table 8 presents descriptive statistics for the study sample. About 50% of the respondents were female and 20% were classified as emerging adults (i.e., 15-24 years of age). Regarding substance use, 8.2% of individuals in the full sample endorsed using cannabis at least once per month (See Appendix A for statistical rationale for the operationalization of cannabis use frequency), 8.0% of the sample met criteria for chronic alcohol use (i.e., endorsed drinking 12 or more drinks per week), 22.3% endorsed binge drinking (5 or more drinks in a sitting) at least once a month, and 2.9% endorsed using other illicit substances within the past 12 months. In the 2012 sample, 8.8% reported daily cigarette use. About 5.4% of the sample met criteria for MDE in the past 12 months and 4.3% endorsed suicidal thoughts while 0.7% endorsed attempts in the last 12 months. Psychological distress was highly positively skewed with most respondents endorsing little to no distress over the past month, although 3.1% of the sample reported scores of 20 and over (indicative of at least mild anxiety and/or depressive symptoms).

Table 9 presents descriptive statistics for the primary study variables by year, age group, and sex. The following results are based on independent t-tests not depicted in Table 2 (available on request). The noted differences in this paragraph reached statistical significance at $p<0.05$. For cannabis use, emerging adults were significantly more likely to report monthly cannabis use than young and middle aged adults. For example, in 2012 22.6% of male and 11.8% of female emerging adults reported monthly use while the corresponding estimates for young and middle aged adults, were 10.0% and 3.7%, respectively. Significant increases in use were found between 2002 and 2012 only among young and middle aged adults (e.g. from 7.4 to 10.0% for males and 2.5 to 3.7% for females). Females within their respective developmental age groups were less likely to report monthly cannabis use compared to males. In regards to emotional problems, females were more likely to report suicidal thoughts and attempts, experience MDE, and report higher levels of psychological distress in both 2002 and 2012. Emerging adults were more likely report suicidal thoughts and attempts in 2012 compared to 2002; 2.9% of male emerging adults reported suicidal

thoughts or attempts in 2002 compared to 5.1% in 2012, and 5.1% of female emerging adults in 2002 compared to 6.1% in 2012 reported suicidal thoughts or attempts. In contrast, young and middle-aged adults were less likely to report suicidal thoughts or attempts in 2012 compared to young and middle-aged adults in 2002 (males 4.3% in 2002 to 3.1% in 2012; females 6.0% in 2002 to 3.4% in 2012). There was no significant difference in rates of MDE or levels of psychological distress between 2002 and 2012 within developmental age groups, biological sex groups, or sex by age groups.

Table 10 presents correlations between substance use and mental health variables. All substance use and mental health variables were significantly positively correlated with one another (all $p<0.0001$). Most correlations were small in magnitude (i.e. <0.3) with the exception of monthly cannabis use, which was moderately correlated with other drug use ($\varphi = 0.37$), and correlations between the mental health variables (i.e. suicidal thoughts or attempts, MDE, and psychological distress), which were moderately correlated with each other (φ /r_{pb} 0.31 to 0.44).

Monthly Cannabis Use by Time

See Table 11 for the results of step-wise binary logistic regression models examining the association between monthly cannabis use and suicidal thoughts and attempts. Across all models, there was a lower odds of suicidal thoughts and attempts in 2012. In model 1, adjusted for year, developmental age, and biological sex, individuals who reported using cannabis at least once a month were 2.86 times (95% CI 2.39, 3.42) more likely to report suicidal thoughts and attempts compared to individuals who never used cannabis or used less than once a month. Model 2 includes the cannabis use-by-time interaction. The association between cannabis use and suicidal thoughts and attempts was stronger in 2012, compared to 2002 (OR 1.59 [95% CI 1.11, 2.27]). For individuals who used cannabis monthly in 2002, the odds of reporting suicidal thoughts and attempts was 2.24 (95% CI 1.82, 2.76) while in 2012, the odds of suicidal thoughts and attempts was 3.56 (95% CI 2.49, 5.08). See Appendix B for the interaction calculations.

Three-way interactions between cannabis use, time, and developmental period or biological sex were not statistically significant. Suicidal thoughts and attempts increased between 2002 and 2012 for emerging adults but monthly cannabis use did not moderate this association (i.e. no evidence of a 3-way interaction) (model 2A). Similarly, although being female was associated with a higher likelihood of experiencing suicidal thoughts or attempts in all models, there was no evidence to suggest that this association differed across time and/or by monthly use of cannabis (model 2B). Therefore, since neither developmental age

nor biological sex moderated the temporal association between cannabis use and time, these interaction terms were not carried forward to further adjusted models.

Model 3 includes other substance use variables. The main effect of cannabis use remained even after adjusting for other substance use (OR 1.56 [95% CI 1.20, 2.02]). Similarly, the interaction term between cannabis use and time remained statistically significant, even after adjusting for other substance use variables (OR 1.64 [95% CI 1.15, 2.34]). Lastly, controlling for proxies of SES, including total household income (model 4A) and role function (model 4B), did not significantly alter these cannabis use-by-time associations for suicidal thoughts and attempts; nor the main effects for cannabis use

The same stepwise approach was performed for MDE yielding similar results compared to models looking at suicidal thoughts and attempts. Table 12 presents results of step-wise binary logistic regression models examining the association between monthly cannabis use and MDE. Mirroring the descriptive statistics, there was no difference in the likelihood of MDE between 2002 and 2012 across all models. In model 1, individuals who reported using cannabis at least once a month were more likely to report MDE than individuals who never used cannabis or used less than once a month (OR 2.93 [95% CI 2.47, 3.47]). Model 2 demonstrates a stronger relationship between use and MDE in 2012 compared to 2002 (OR 1.55 [95% CI 1.12, 2.13]). For individuals who used cannabis monthly in 2002, the odds of experiencing MDE was 2.27 (95% CI 1.84, 2.80), while in 2012 the odds MDE was 3.51 (95% CI 2.75, 4.48). See Appendix B for the interaction calculations. Emerging adults who used cannabis at least monthly were more likely to experience MDE than young and middle-aged adults (OR 1.54 [95% CI 1.11, 2.14]) but the strength of this association remained similar across time (model 2A). Female sex was associated with a higher likelihood of experiencing MDE, but there was no evidence to suggest that this association differed across time and/or by monthly use of cannabis (model 2B). Since neither variable changed the cannabis use-by-time effect, three-way interactions (and the associated lower order interactions) were not carried forward for subsequent models. The two-way cannabis use-by-time effects remained after adjusting for other substance use (model 3) and proxies of SES (models 4A and 4B).

See Table 13 for results of step-wise linear regression models examining the association between monthly cannabis use and psychological distress. Models produced similar results to suicidal thoughts and attempts and MDE. In most models, there was no difference in psychological distress scores between 2002 and 2012. Individuals who reported using cannabis at least once a month reported

higher levels of psychological distress compared to individuals who never used cannabis or used less than once a month (model 1). The association between cannabis use and psychological distress was stronger in 2012, compared to 2002 (model 2). Individuals who used cannabis monthly in 2002 reported psychological distress scores on average 2.34 points higher (95% CI 2.00, 2.69) than those who used less than once a month or never, while in 2012 individuals who used cannabis monthly scored 2.94 points higher (95% CI 2.47, 3.40). See Appendix B for the interaction calculations. Although emerging adults reported higher psychological distress scores across models, developmental age did not impact the cannabis use-by-time effect (model 2A). Model 2B shows females report higher psychological distress scores compared to males (b=0.59 [95% CI 0.39, 0.78]), these sex differences became more pronounced in 2012 compared to 2002 (b=0.39 [95% CI 0.06, 0.71]), and females who used cannabis at least monthly reported psychological distress scores on average 1.03 (95% CI 0.28, 1.78) scale points higher than males who used cannabis at least monthly, but this association did not get stronger over time (i.e. no evidence of a three-way interaction). Therefore these higher and lower order interactions were not carried forward for subsequent models. The two way cannabis-by-time effects remained after adjusting for other substance use (model 3) and total household income (model 4A), but, when adjusting for role function (model 4B), time-by-cannabis effects became non-significant.

False Discovery Rate (FDR) calculations were employed for the primary models (Model 2). After adjusting for multiple testing (m=5), all effects remained significant for suicidal thoughts and attempts and MDE but the time-by-cannabis use interaction no longer met statistical significance for psychological distress (actual p=0.0425; new critical p=0.04). See Appendix C for FDR calculations.

Clinically significant effect sizes were determined *a priori*; ORs of 1.5 and a change in psychological distress by 2.5 points were considered clinically meaningful differences. In 2002, cannabis use produced clinically meaningful effect estimates for suicidal thoughts and attempts and MDE at both ends of the confidence intervals. However, in 2002, psychological distress produced estimates just below *a priori* cut offs (2.34 (95% CI 2.00, 2.69). In 2012, cannabis use produced clinically meaningful effects estimates for all outcomes at both ends of the CI (i.e. even at lower limits of the CI, effect sizes were clinically relevant), with ORs for suicidal thoughts and attempts and MDE surpassing *a priori* cut offs.

Cigarette Smoking Sensitivity Analysis

See Table 14 for results of cigarette smoking sensitivity analyses on the association between cannabis use and emotional problems only using 2012 data. The base model (i.e. Model 1) was adjusted for other substance use variables including chronic alcohol use, acute alcohol use, other illicit drug use, and unlike previous models, cigarette smoking. After adjusting for cigarette smoking (both occasional and daily smoking), at least monthly cannabis use remained significantly positively related to suicidal thoughts attempts (OR 1.96 [95% CI 1.38, 2.79]), MDE (OR 2.03 [95% CI 1.51, 2.73]), and psychological distress (b=1.71 [95% CI 1.21, 2.21]). Since cigarette smoking was only asked in 2012, I was unable to determine the robustness of the cannabis use-by-time effect, however, these sensitivity analyses provide evidence to support that cannabis use is related to emotional mental health outcomes over and above alcohol, other illicit substance use, and cigarette use.

Commonality Analysis

See the column labels "Percentage" in Table 15 for the variance in psychological distress uniquely attributed to particular type of substance use. Overall, substance use appears to be explaining a very small percentage of the variance in K10 psychological distress scores (C123 2.6%). However, of the variance that is being explained, cannabis use contributes to 1.9% of this variance independent of and in combination with other substance use (U1 R^2=0.019). Importantly, cannabis use contributes the largest amount of unique variance (U1=0.78%) when compared to alcohol use (U2=0.11%), and other illicit substance use (U3=0.58%). This being said, 1.09% (absolute) of the variance cannabis explains is shared variance with alcohol (C12=0.17%), other drugs (C13=0.67%), and both alcohol and other drugs (C123=0.26%). About 42% (calculation=0.78 [U1 %]/1.9 [U1 R^2]) of initial effect remains unique to cannabis. See Figure 9 for a visual depiction of the unique and shared variance in psychological distress scores for particular types of substance use.

Summary

Cannabis use is associated with increased likelihood of experiencing suicidal thoughts and attempts, MDE, and higher psychological distress. The association between cannabis use and MDE and suicide has strengthened over time, particularly for MDE and suicidal thoughts and attempts. These effects remained even after controlling for other substance use. Female biological sex and developmental age do not moderate this temporal trend.

Chapter Three References

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Thesis Results: Tables and Figures

Table 8
Descriptive Statistics, n=43,466[2]

Total sample	% or mean (SD)
2012	51.9%
Demographics	
Age	
Age in years	37.9 (0.05)
Emerging Adult	20.1%
Young Adult	20.4%
Middle aged Adult	59.5%
Female	50.1%
Employed	71.4%
Total Household Income	9.1[3] (0.02)
Student	17.5%
Education	
High-school or lower	44.8%
Trade certificate or diploma	10.4%
Non-university certificate or diploma	19.3%
University certificate below bachelor's level	3.9%
Bachelor's degree	15.1%
University degree or certificate above bachelor's degree	6.5%
Substance Use	
Cannabis use at least once per month	8.2%
Chronic Alcohol Use	8%
Acute (Binge) Alcohol Use (continuous)	0.9 (0.02)
Acute (Binge) Alcohol Use at least once per month	22.3%
Any Other Illicit Drug Use (past 12 months)	2.9%
Smoking (only 2012)	
Occasional	3.4%
Daily	8.8%
Mental Health	
MDE (past 12 months)	5.4%
Past 12 month Suicidal Thoughts and Attempts	
Suicidal Thoughts	4.3%
Suicide Attempt	0.7%
K10	
Total Score	5.6 (0.05)
Less than 20	96.9%
20 or more	3.1%

[2] Weighted and bootstrapped for population based estimates.

[3] Income measured ordinally. A score of '9' was reflective of total household income of $50,000 to less than $60, 000.

Table 9

Descriptive Statistics Stratified by Year, Developmental Age, and biological Sex[1]

	2002				2012			
	Emerging Adult		Young & Middle		Emerging Adult		Young & Middle	
	Male	Female	Male	Female	Male	Female	Male	Female
	Cannabis							
At least monthly Cannabis use	22.6%	12.1%	7.4%	2.5%	22.6%	11.8%	10.0%	3.7%
	Mental Health Outcome Variables							
Suicidal Thoughts and/or Behaviours	2.9%	5.1%	4.3%	6.0%	5.1%	6.6%	3.1%	3.4%
Major Depressive Episode	4.4%	8.5%	3.8%	6.4%	5.3%	8.8%	3.8%	6.2%
K10 score	6.22 (0.134)	7.16 (0.157)	5.11 (0.077)	5.51 (0.075)	6.04 (0.178)	7.08 (0.198)	4.90 (0.100)	5.74 (0.130)
K10 <20	98.0%	95.3%	97.5%	96.9%	97.4%	94.7%	98.0%	96.0%
K10 >=20	2.0%	4.7%	2.5%	3.1%	2.6%	5.3%	2.0%	4.0%

Note. T-tests were done for all two-way comparisons. Results of t-tests not presented in this table but available upon request.

Table 10

Correlations (Phi and Point Biserial correlations) Between Key Study Variables[1]

	Monthly Cannabis Use	Chronic Alcohol	Binge Drinking	Other Drugs	Suicide	MDE	K10 Psych Distress
Monthly Cannabis	1						
Chronic Alcohol	0.17	1					
Binge Drinking	0.27	0.52	1				
Other Drugs	0.37	0.13	0.21	1			
Suicide	0.07	0.04	0.03	0.09	1		
MDE	0.08	0.02	0.03	0.11	0.36	1	
K10 Psych Distress	0.14	0.04	0.08	0.13	0.31	0.44	1

Note. Correlations <0.3, 0.3 to <0.5, and >=0.5 are interpreted as low degree, moderate degree, and high degree respectively. All correlations are significant at p<0.001.

Table 11

Stepwise Logistic Regression Models Presenting The Strength Of The Association Between Cannabis Use And Suicidal Thoughts And Attempts

Effect	Base Model (Model 1)	Time Model (Model 2)	Emerging Adult by Time Model (Model 2A)	Female by Time Model (Model 2B)	Time Model Adjusted 1 (Model 3)	Time Model Adjusted 2 (Model 4A)	Time Model Adjusted 3 (Model 4B)
2012 (ref 2002)	0.74*** (0.64, 0.85)	0.68*** (0.58, 0.80)	0.58*** (0.48, 0.71)	0.81 (0.63,1.05)	0.68*** (0.58, 0.81)	0.74*** (0.62, 0.87)	0.67*** (0.56, 0.79)
Emerging Adulthood	1.02 (0.88, 1.18)	1.03 (0.88, 1.19)	0.63*** (0.51, 0.78)	1.02 (0.88,1.19)	0.98 (0.83, 1.14)	0.98 (0.83, 1.16)	1.09 (0.92, 1.28)
Female Sex	1.48*** (1.28, 1.71)	1.48*** (1.28, 1.71)	1.45*** (1.24, 1.70)	1.57*** (1.30, 1.89)	1.56*** (1.35, 1.81)	1.47*** (1.26, 1.71)	1.39*** (1.18, 1.99)
Cannabis Use (>= monthly)	2.86*** (2.39, 3.42)	2.24*** (1.82, 2.76)	2.40*** (1.86, 3.10)	2.19*** (1.63, 2.95)	1.56*** (1.20, 2.02)	1.38* (1.06, 1.80)	1.54** (1.18, 1.99)
2012*Cannabis		1.59*** (1.11, 2.27)	1.26 (0.88, 1.81)	1.17 (0.72, 1.90)	1.64*** (1.15, 2.34)	1.65** (1.14, 2.38)	1.51* (1.05, 2.17)
Emerging*Cannabis			1.18 (0.80, 1.75)				
2012*Emerging			2.26*** (1.51, 3.39)				
2012*Emerging*Cannabis			1.12 (0.71, 1.77)				
Female*Cannabis				0.75 (0.53, 1.05)			
2012*Female				1.10 (0.73, 1.67)			
2012*Female*Cannabis				1.83 (0.96, 3.50)			

Other Drugs					2.59*** (1.90, 3.55)	2.49*** (1.80, 3.45)	2.53*** (1.85, 3.45)
Chronic Alcohol					1.62*** (1.25, 2.10)	1.61*** (1.22, 2.11)	1.53** (1.17, 2.01)
Binge Alcohol					1.00 (0.94, 1.06)	1.01 (0.94, 1.07)	1.02 (0.96, 1.09)
Income						0.86*** (0.84, 0.89)	
Function Part Time							0.71** (0.57, 0.88)
Function Full Time							0.45*** (0.38, 0.54)
Notes. Results are presented as ORs and 95% CIs[1]; *p<0.05, **p<0.01, ***p<0.001							

Table 12

Stepwise Models Presenting the Strength of the Association Between Cannabis Use and MDE

Effect	Base Model (Model 1)	Time Model (Model 2)	Emerging Adult by Time Model (Model 2A)	Female by Time Model (Model 2B)	Time Model Adjusted 1 (Model 3)	Time Model Adjusted 2 (Model 4A)	Time Model Adjusted 3 (Model 4B)
2012 (ref 2002)	0.98 (0.87, 1.12)	0.92 (0.80, 1.06)	0.91 (0.78, 1.06)	0.90 (0.72, 1.13)	0.91 (0.80, 1.05)	1.03 (0.89, 1.19)	0.89 (0.77, 1.02)
Emerging Adulthood	1.16*** (1.00, 1.33)	1.16* (1.01, 1.34)	1.11 (0.90, 1.36)	1.17* (1.01, 1.34)	1.08 (0.93, 1.25)	1.02 (0.87, 1.19)	1.21* (1.04, 1.41)
Female Sex	1.94*** (1.71, 2.20)	1.94*** (1.71, 2.21)	1.92*** (1.67, 2.19)	1.93*** (1.62, 2.29)	2.03*** (1.78, 2.33)	1.91*** (1.65, 2.20)	1.82*** (1.57, 2.10)
Cannabis Use (>= monthly)	2.93*** (2.47, 3.47)	2.27*** (1.84, 2.80)	2.21*** (1.69, 2.90)	2.26*** (1.71, 2.98)	1.48** (1.15, 1.90)	1.36* (1.05, 1.77)	1.41** (1.09, 1.82)
2012*Cannabis		1.55*** (1.12, 2.13)	1.08 (0.75, 1.55)	1.61* (1.04, 2.49)	1.64** (1.19, 2.28)	1.60** (1.13, 2.26)	1.58** (1.13, 2.20)
Emerging* Cannabis			1.54* (1.11, 2.14)				
2012*Emerging			1.00 (0.68, 1.48)				
2012*Emerging* Cannabis			1.11 (0.73, 1.69)				
Female* Cannabis				1.03 (0.76, 1.39)			
2012*Female				1.01 (0.68, 1.50)			
2012*Female* Cannabis				0.92 (0.50, 1.70)			
Other Drugs					3.28*** (2.47, 4.34)	3.17*** (2.35, 4.27)	3.17*** (2.38, 4.22)

Chronic Alcohol					1.21 (0.95, 1.53)	1.13 (0.88, 1.47)	1.14 (0.90, 1.46)
Binge Alcohol					1.02 (0.96, 1.08)	1.04 (0.98, 1.10)	1.05 (0.99, 1.11)
Income						0.86*** (0.84, 0.88)	
Function Part Time							0.67*** (0.54, 0.82)
Function Full Time							0.44*** (0.38, 0.51)
Notes. Results are presented as ORs and 95% CIs[1]; *p<0.05, **p<0.01, ***p<0.001							

Table 13

Stepwise Models Presenting the Strength of the Association Between Cannabis Use and Psychological Distress

Effect	Base Model (Model 1)	Time Model (Model 2)	Emerging Adult by Time Model (Model 2A)	Female by Time Model (Model 2B)	Time Model Adjusted 1 (Model 3)	Time Model Adjusted 2 (Model 4A)	Time Model Adjusted 3 (Model 4B)
2012 (ref 2002)	-0.06 (-0.23, 0.11)	-0.11 (-0.28, 0.07)	-0.08 (-0.28, 0.12)	-0.31*** (-0.53, -0.09)	-0.14 (-0.31, 0.03)	0.10 (-0.08, 0.28)	-0.20* (-0.37, -0.03)
Emerging Adulthood	1.00*** (0.81, 1.19)	1.01*** (0.82, 1.20)	1.13*** (0.89, 1.37)	1.00*** (0.81, 1.18)	0.90*** (0.71, 1.09)	0.71*** (0.51, 0.91)	1.11*** (0.92, 1.29)
Female Sex	0.88*** (0.71, 1.05)	0.88*** (0.71, 1.05)	0.83*** (0.65, 1.01)	0.59*** (0.39, 0.78)	1.04*** (0.86, 1.21)	0.92*** (0.74, 1.10)	0.82*** (0.64, 1.00)
Cannabis Use (>= monthly)	2.68*** (2.38, 2.98)	2.34*** (2.00, 2.69)	2.45*** (1.99, 2.92)	1.98*** (1.57, 2.38)	1.47*** (1.09, 1.85)	1.27*** (0.86, 1.68)	1.41*** (1.04, 1.79)
2012* Cannabis		0.60* (0.02, 1.17)	0.64* (0.06, 1.23)	0.51 (-0.14, 1.15)	0.71* (0.14, 1.28)	0.63** (0.03, 1.23)	0.55 (-0.02, 1.13)
Emerging* Cannabis			-0.33 (-0.96, 0.30)				
2012*Emerging			-0.41 (-0.83, 0.02)				
2012*Emerging* Cannabis			0.51 (-0.01, 1.03)				
Female* Cannabis				1.03** (0.28, 1.78)			
2012*Female				0.39* (0.06, 0.71)			
2012*Female* Cannabis				0.58 (-0.66, 1.82)			
Other Drugs					2.49*** (1.91, 3.06)	2.37*** (1.78, 2.96)	2.39*** (1.82, 2.97)

Chronic Alcohol					0.01 (-0.32, 0.34)	-0.10 (-0.43, 0.23)	-0.10 (-0.42, 0.22)
Binge Alcohol					0.23*** (0.16, 0.30)	0.29*** (0.21, 0.36)	0.28*** (0.21, 0.35)
Income						-0.40*** (-0.44, -0.36)	
Function Part Time							-1.67*** (-2.07, -1.26)
Function Full Time							-2.18*** (-2.51, -1.85)
Notes. Results are presented as ORs and 95% CIs[1]; *p<0.05, **p<0.01, ***p<0.001							

Table 14

Adding In Tobacco Use Using the 2012 Sample to Determine the Independent Main Effects of Cannabis Use Over and Above Other Substances

	Suicidal Thoughts and Attempts	MDE	K10 (raw)
Emerging Adulthood	1.58*** (1.22, 2.04)	1.17 (0.94, 1.45)	0.98*** (0.69, 1.27)
Female Sex	1.36* (1.04, 1.76)	2.02*** (1.61, 2.53)	1.26*** (0.99, 1.54)
Cannabis use at least once per month	1.96*** (1.38, 2.79)	2.03*** (1.51, 2.73)	1.71*** (1.21, 2.21)
Other Illicit Drugs	2.97*** (1.87, 4.70)	3.84*** (2.55, 5.76)	2.84*** (1.98, 3.71)
Chronic Alcohol Use	1.20 (0.79, 1.81)	0.90 (0.62, 1.31)	-0.51* (-1.00, -0.02)
Acute (Binge) Alcohol Use	0.92 (0.83, 1.03)	0.99 (0.91, 1.09)	0.21*** (0.10, 0.32)
Smoking Occasionally	1.70* (1.01, 2.87)	1.03 (0.67, 1.58)	0.44 (-0.05, 0.92)
Smoking Regularly	1.81*** (1.33, 2.47)	1.82*** (1.44, 2.30)	1.76*** (1.28, 2.23)
Note. *p<0.05, **p<0.01, ***p<0.001			

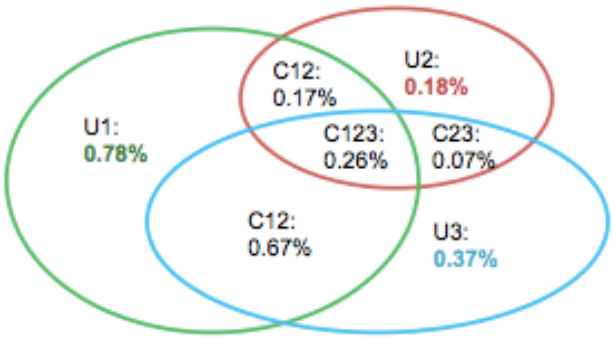
Table 15

The Variance in Psychological Distress that is Attributed to each Partially Adjusted Regression Model (R^2) Followed by the Percentage (%) of Variance Uniquely Attributed to each Particular Type of Substance Use

	Substance	R^2	Unique %
Total Sample *controlled for year			
U1	CANNABIS	0.019	0.78
U2	ALCOHOL	0.006	0.11
U3	DRUGS	0.016	0.58
C12	CANNABIS & ALCOHOL	0.020	0.17
C13	CANNABIS & DRUGS	0.025	0.67
C23	ALCOHOL & DRUGS	0.019	0.07
C123	CANNABIS&ALCOHOL& DRUGS	0.026	0.26

Notes. U=unique, C=common, 1=cannabis, 2=alcohol (both chronic and acute), 3=other illicit drugs.

Figure 9. Substance use overlap commonality analysis (psychological distress).



APPENDIX A

Operationalization of Monthly Cannabis Use

Appendix A, Table 1 presents descriptive statistics regarding frequency of use among the full sample (2002 and 2012 combined) and Table 2 presents frequencies stratified by year, developmental age, and biological sex. Appendix A, Table 3 shows results for mental health outcomes regressed on cannabis use categories of less than once a month, one to three times per month, once per week, more than once per week, and daily use adjusted for year, developmental age, and biological sex. For all outcomes, even using cannabis less than once a month was related to a significant increase in experiencing poor mental health compared to individuals who did not endorse using cannabis at all. Generally, a dose-response relationship emerged with daily use being the strongest correlate, although confidence intervals overlapped. The confidence interval for daily use overlapped with cannabis frequency categories of at least monthly use, but not less than monthly use for suicide and MDE. For the K10, daily use overlapped with more than once per week but was significantly larger than weekly or less than weekly use. From this, I collapsed cannabis use into a binary variable for future models to create categories of (0) less than monthly use or non-use and (1) at least monthly use.

Appendix A, Table 1

Prevalence of Cannabis use Frequency in the full Sample

Past 12 months	14.2%
Less than once per month	6%
1-3 times per month	2.6%
Once per week	1.5%
More than once per week	2.4%
Everyday	1.8%

Appendix A, Table 2

Prevalence of Cannabis use Frequency stratified by year, developmental age, and biological sex[1]

	2002				2012			
	Emerging Adult		Young & Middle		Emerging Adult		Young & Middle	
	Male	Female	Male	Female	Male	Female	Male	Female
Cannabis								
Never	64.8%	73.2%	86.8%	93.6%	67.6%	78.7%	84.6%	92.8%
Less than monthly	12.5%	14.7%	5.9%	3.8%	9.8%	9.5%	5.3%	3.5%
1-3 times a month	7.2%	4.8%	2.2%	1.1%	7.7%	4.4%	2.8%	1.0%
Once a week	4.4%	1.9%	1.4%	0.5%	3.8%	1.4%	2.0%	0.6%
More than once a week	6.9%	3.3%	2.3%	0.5%	6.3%	2.7%	2.7%	1.2%
Everyday	4.0%	2.1%	1.5%	0.5%	4.9%	3.3%	2.5%	1.0%

Appendix A, Table 3

The relationship between Cannabis Frequency and emotional problems[1]

	Suicidal Thoughts and Attempts	MDE	K10 (raw)
Cannabis use less than 1/month	1.85 (1.46, 2.35)	1.91 (1.56, 2.34)	1.52 (1.18, 1.86)
Cannabis use 1-3 times per month	2.57 (1.85, 3.56)	2.34 (1.74, 3.14)	1.85 (1.39, 2.31)
Cannabis use 1 per week	2.14 (1.35, 3.40)	2.52 (1.71, 3.71)	2.18 (1.53, 2.84)
Cannabis use more than once a week	3.14 (2.36, 4.19)	3.35 (2.50, 4.47)	3.22 (2.66, 3.78)
Cannabis use daily	4.56 (3.33, 6.23)	4.74 (3.49, 6.42)	4.21 (3.51, 4.90)

Notes. Adjusted for year, developmental age, and biological sex. All effects significant at $p<0.001$.

APPENDIX B

Interaction Calculations

1. Suicidal Thoughts and attempts

Interaction Effect Size

β_{MJ}= 0.8071
$\beta_{MJ*year}$= 0.4623
$\beta_{Interaction} = \beta_{MJ}+\beta_{MJ*year}$=1.2694
$OR_{interaction}$=EXP ($\beta_{MJ}+\beta_{MJ*year}$) = EXP (1.2694) = 3.56

Interaction Confidence Interval

Var_{MJ} = (SE_{MJ}^2) = 0.1067^2 = 0.01138489
$Var_{MJ*year}$ = ($SE_{MJ*year}^2$) = 0.1816^2 = 0.03297856
$Cov_{MJ, year*MJ}$ = -0.01169
$Var_{interaction}$ = Var_{MJ+} $Var_{MJ*year}$ +2($Cov_{MJ, year*MJ}$)
= 0.01138489+0.03297856+2*-0.01169 = 0.03297856
$SE_{interaction}$ = $\sqrt{Var}$ = $\sqrt{0.03297856}$ = 0.1816
In($CI_{interaction\_low}$) = $\beta_{Interaction}$ – (1.96* $SE_{interaction}$)
= 1.2694 – (1.96*0.1816)
= 0.913464
= EXP(In[CI])
= EXP(0.913464)
= 2.49
In ($CI_{interaction\_high}$) = $\beta_{Interaction}$ + (1.96* $SE_{interaction}$)
= 1.2694 + (1.96*0.1816)
= 1.625336
= EXP(In[CI])
= EXP (1.625336)
= 5.08

2. MDE

Interaction Effect Size

β_{MJ}= 0.8206
$\beta_{MJ*year}$= 0.4353
$\beta_{Interaction} = \beta_{MJ}+\beta_{MJ*year}$= 1.2559
$OR_{interaction}$=EXP ($\beta_{MJ}+\beta_{MJ*year}$) = EXP (1.2559) = 3.51

Interaction Confidence Interval

Var_{MJ} = (SE_{MJ}^2) = 0.1066^2 = 0.01136356

$Var_{MJ*year}$ = $(SE_{MJ*year}^2)$ = 0.1637^2 = 0.02679769
$Cov_{MJ,\ year*MJ}$ = -0.01128
$Var_{interaction}$ = Var_{MJ+} $Var_{MJ*year}$ +2($Cov_{MJ,\ year*MJ}$)
= 0.01136356+0.02679769+2*-0.01128
= 0.01560125

$SE_{interaction}$ = $\sqrt{Var}$ = $\sqrt{0.01560125}$= 0.124904964
In($CI_{interaction\_low}$) = $\beta_{Interaction}$ – (1.96* $SE_{interaction}$)
= 1.2559 – (1.96*0.124904964)
= 1.011086271
= EXP(In[CI])
= EXP(1.011086271)
= 2.75

In ($CI_{interaction\_high}$) = $\beta_{Interaction}$ + (1.96* $SE_{interaction}$)
= 1.2559+ (1.96*0.124904964)
= 1.500713729
= EXP(In[CI])
= EXP (1.500713729)
= 4.48

3. Psychological Distress

Interaction Effect Size
β_{MJ}= 2.3443453
$\beta_{MJ*year}$= 0.5956305
$\beta_{Interaction}$ = β_{MJ}+$\beta_{MJ*year}$=2.9399758

Interaction Confidence Interval
Var_{MJ} = (SE_{MJ}^2) = 0.1772375^2 = 0.031413131
$Var_{MJ*year}$ = $(SE_{MJ*year}^2)$ = 0.29287842^2 = 0.085777769
$Cov_{MJ,\ year*MJ}$ = -0.030903025
$Var_{interaction}$ = Var_{MJ+} $Var_{MJ*year}$ +2($Cov_{MJ,\ year*MJ}$)
= 0.031413131+0.085777769+2*-0.030903025 = 0.05538485
$SE_{interaction}$ = $\sqrt{Var}$ = $\sqrt{0.05538485}$= 0.235339861
In($CI_{interaction\_low}$) = $\beta_{Interaction}$ – (1.96* $SE_{interaction}$)
= 2.9399758– (1.96*0.235339861)
= 2.478709672
In ($CI_{interaction\_high}$) = $\beta_{Interaction}$ + (1.96* $SE_{interaction}$)
= 2.9399758+ (1.96*0.235339861)
= 3.401241928

APPENDIX C

FDR Calculations

Appendix B, Table 1

FDR Calculations for Suicidal Thoughts and Attempts (model 2)

	p value	k	m	alpha	alpha (k/m)	stat-p
year	<.0001	1	5	0.05	0.01	0.0099
emerging_adult	0.7326	5	5	0.05	0.05	-0.6826
biosex	<.0001	2	5	0.05	0.02	0.0199
mj_month	<.0001	3	5	0.05	0.03	0.0299
year_mjm	0.0112	4	5	0.05	0.04	0.0288

Appendix B, Table 2

FDR Calculations for MDE (model 2)

	p value	k	m	alpha	alpha (k/m)	stat-p
year	0.2287	5	5	0.05	0.05	0.0499
emerging_adult	0.0359	4	5	0.05	0.04	0.0041
biosex	<.0001	2	5	0.05	0.02	0.0199
mj_month	<.0001	1	5	0.05	0.01	0.0099
year_mjm	0.0081	3	5	0.05	0.03	0.0219

Appendix B, Table 3

FDR Calculations for Psychological Distress (model 2)

	p value	k	m	alpha	alpha (k/m)	stat-p
year	0.2276	5	5	0.05	0.05	-0.1776
emerging_adult	<.0001	1	5	0.05	0.01	0.0099
biosex	<.0001	2	5	0.05	0.02	0.0199
mj_month	<.0001	3	5	0.05	0.03	0.0299
year_mjm	0.0425	4	5	0.05	0.04	-0.0025

Chapter Four: Discussion

General Overview

This secondary analysis of the 2002 and 2012 CCHS-MH surveys found that Canadians 15 to 60 years of age who used cannabis at least monthly were more likely to experience suicidal thoughts and attempts, MDE, and higher levels of psychological distress than those who used less than monthly or not at all. The association between cannabis use and each of these mental health related outcomes was stronger in 2012, compared to 2002. Returning to the study objectives, this study found that:

1. The positive association between cannabis use and emotional problems strengthened over time, particularly for MDE and suicidal thoughts and attempts.
2. Developmental age did not moderate these temporal associations.
3. Female sex did not moderate these temporal associations.
4. These temporal associations remained after controlling for alcohol and other illicit substance use.
5. These temporal associations remained after controlling for proxies of SES.
6. The increased odds of emotional problems associated with cannabis use remained after controlling for tobacco use in the 2012 sample.

The temporal change in the strength of association between cannabis use and emotional problems adds novel insights to the existing literature. Due to this novelty, the cannabis use-by-time effects cannot be directly compared to existing evidence, although they do support the *a priori* hypotheses. In contrast, developmental age and biological sex did not moderate this temporal association, and the findings are not consistent with the hypotheses linked to age and sex.

Other effects were consistent with pre-existing literature. Similar to previous studies, rates of MDE (Pearson, Janz, & Ali, 2013) and psychological distress (Patten et al., 2014) remained similar over time while suicidal related outcomes decreased among young and middle-aged Canadian adults (Sareen et al., 2016) but increased for younger Canadians (Skinner & McFaull, 2012; Although this study found different patterns dependent on gender). As previously documented, females were more likely to experience emotional problems than males (Pearson et al., 2013) and emerging adults were more likely to experience emotional problems than older populations (Pearson et al., 2013). This analysis also found a dose-response relationship between cannabis use and emotional problems that has been replicated in other samples (Borges, Bagge, & Orozco, 2016; Lev-Ran, Le Foll, McKenzie, & Rehm, 2012; Lev-

Ran et al., 2014) and females who used cannabis at least monthly were more likely to experience psychological distress (Danielsson, Lundin, Allebeck, & Agardh, 2016) compared to males who used cannabis. Another novel finding, although consistent with initial hypotheses, was the stronger association between cannabis use and MDE among emerging adults but this association was not found for suicidal thoughts or attempts or psychological distress. The stronger association between cannabis use and MDE was not consistent across emotional problems, which may be due to differences in approaches to measurement (i.e. diagnostic interviews versus self-reported items) or the conceptualization of emotional problems (i.e. the symptom of suicide thoughts or attempts, a broader but still narrow definition of MDE, or a broad conceptualization of general psychological distress). In general, though not the primary objectives of this analysis, there were many consistencies between this study and pre-existing evidence.

There are several plausible explanations for the increased strength of the association between cannabis use and emotional problems between 2002 and 2012. Evidence on the changes in cannabis composition, perceptions and motivations for cannabis use, and patterns of cannabis use reflect potential mechanisms for the observed increased association over time. The following discussion explores potential mechanisms of this temporal effect - including changes in cannabis composition, perceptions and motivations for cannabis use, and patterns of cannabis use – and the strengths and limitations of this analysis, followed by implications for practice and research.

Postulating Mechanisms of Temporal Effects

Potency. As discussed in Chapter One, the potency of both medical and recreational cannabis has dramatically increased over the past decade: on average, levels of THC have increased while levels of CBD have decreased (Cascini, Aiello, & Di Tanna, 2012; CBC Marketplace, 2016; ElSohly et al., 2016; Mammen, de Freitas, Rehm, & Rueda, 2017). Several double blind randomized controlled trials (RCTs) comparing the effects of THC and CBD have demonstrated that: (a) THC administration, without CBD, results in increased anxiety and risk of transient psychosis, (b) CBD administration, without THC, either results in no effect or improvements in anxiety and mood state, and (c) CBD in conjunction with THC dampens the negative psychoactive and anxiogenic effects seen in THC administration alone (Bhattacharyya et al., 2009; Fusar-Poli et al., 2009; Hindocha et al., 2015; Hunault et al., 2014; Martin-Santos et al., 2012; Winton-Brown et al., 2011). In general, THC has been associated with poorer mental health outcomes especially when paired with low CBD.

There is also some evidence to suggest that repeated administration of cannabis down-regulates or desensitizes CB1 receptors (Hirvonen et al., 2012; Imperatore et al., 2015; Weinstein, Livny, & Weizman, 2016). Since the THC binds more strongly to the CB1 receptors than endogenous cannabinoids, when these receptors are internalized they are more likely to breakdown as opposed to being recycled. As the number of CB1 receptors decreases, the body builds up a tolerance for the rewarding effects of cannabis, altering the structure of the ECS to accommodate the constant stimulation. This tolerance effect, or down-regulation, puts people at a greater risk for mental health concerns (Tambaro, Tomasi, & Bortolato, 2013; Volkow et al., 2014). Acute exposure to cannabis may enhance activation of CB1 receptors and potentially produce desired anxiolytic responses, but chronic administration reduces the number of CB1 receptors and impairs neuronal signalling (including dopamine signalling) resulting in withdrawal that exacerbates emotional symptoms, particularly the risk of depression and dependence (Volkow, Hampson, & Baler, 2017). Therefore, the increase in potency (THC) of cannabis may be driving the increased risk of emotional problems observed over time.

It was hypothesized that this increasing potency would have a greater negative association with emotional problems among emerging adults and females. In emerging adults, this hypothesis was based on THC's disruption of healthy neuromaturation (Dow-Edwards & Silva, 2017; Jacobus, Squeglia, Infante, Bava, & Tapert, 2013; Jacobus et al., 2015; Jacobus, Squeglia, Sorg, Nguyen-Louie, & Tapert, 2014; Medina, Nagel, Park, McQueeny, & Tapert, 2007; Shollenbarger, Price, Wieser, & Lisdahl, 2015; Zalesky et al., 2012). Among females, this hypothesis was based on previous evidence suggesting stronger associations among females postulated to be due to sex differences in the expression of hormones, function of the ECS, and dopamine signalling (Becker, Perry, & Westenbroek, 2012; Craft, Marusich, & Wiley, 2013; Craft, Wakley, Tsutsui, & Laggart, 2012; Fattore et al., 2007; Fattore, Spano, Altea, Fadda, & Fratta, 2010; Fattore, Melis, Fadda, & Fratta, 2014; Krebs-Kraft, Hill, Hillard, & McCarthy, 2010; Moran-Santa Maria, Flanagan, & Brady, 2014; Winsauer et al., 2011). In the present study, I did not find evidece to support these hypotheses –developmental period and sex did not moderate the association between cannabis use, time and emotional problems. Although THC has increased over time, the threshold for THC "toxicity" or the potency that is considered to be harmful, especially in the context of long-term mental health concerns for particular sub-populations, is unknown.

Alternative Explanations.

Frequency of Use. Past month cannabis use in general did not significantly change for emerging adults and increased for young and middle-aged adults between

2002 and 2012 (See Appendix A). Additionally, the proportion of individuals using more regularly increased. Therefore, the temporal increase in the strength of the association between cannabis use and emotional problems may be due to an increase in frequency of use. In this study, point estimates for the strength of the association between frequency of cannabis use and emotional problems were reflective of dose-response relationship, where more than once a week or daily cannabis use produced the largest point estimates (See Appendix A). Previous studies have also found a dose-response association between cannabis use and emotional problems (Borges et al., 2016; Lev-Ran et al., 2012; Lev-Ran et al., 2014). However, there are inconsistencies in existing literature regarding the changes in cannabis use over time in Canada (Boak, Hamilton, Adlaf, & Mann, 2017; Ialomiteanu, Hamilton, Adlaf, & Mann, 2016; Rotermann & Macdonald, 2018) and, overall, there is not enough evidence to be confident of the nature of frequent cannabis use changes over time.

Method of Delivery. Previous studies have found temporal changes in the method of delivery of cannabis, particularly in response to medicalization of cannabis (Borodovsky, Crosier, Lee, Sargent, & Budney, 2016; Lucas, 2012; Shiplo, Asbridge, Leatherdale, & Hammond, 2016). Although the most common method of delivery remains smoking, the use of vaporizers and edibles has been gaining in popularity, and individuals may engage in using multiple methods of delivery or ingestion of cannabis (Boak et al., 2017; Koning, 2010). Different methods are known to yield different "highs" or lengths of onset of action, whereby vaporizing and smoking have similar onsets, magnitudes (including blood THC levels), and durations of "high" (Abrams et al., 2007), while edibles yield longer onset, lower magnitudes, and longer durations of "high" (Health Canada, 2013). There is no current evidence comparing the longer-term mental health implications of different methods of delivery but temporal shifts in methods of delivery may be altering the ways in which cannabis interacts with and impacts the ECS and potentially contributing to this increased association between cannabis use and emotional problems over time.

Medicalization and Changing Perceptions. The number of Canadians using cannabis for medical reasons has dramatically increased since initial medical legalization with over 235,000 registrants in September 2018 (Health Canada, 2018). Medical cannabis can be prescribed for mood and anxiety disorders despite the lack of therapeutic evidence. Although there may be potential for a specific component or type of cannabis to be beneficial for mood due to the interplay with the ECS, there is currently insufficient evidence to make such a claim. A recent systematic review on the medical use of cannabis suggests that medical cannabis poses psychiatric risks and individuals with unstable mood or anxiety disorders should not use medical cannabis, even for the purpose of treating other physical conditions (Hill, 2015). Other reviews note the lack of existing evidence for the use of cannabis for treatment

of behavioural disorders, and if it is being considered, should be considered a last line experimental treatment (Hadland, Knight, & Harris, 2015).

Despite the lack of evidence, there appears to be a correlation between medicalization of cannabis and the perception of mental health benefits of cannabis. In the U.S., in states with medical cannabis, adults with mood and anxiety disorders are more likely to self-medicate with cannabis compared to states without these laws (Sarvet et al., 2018). Additionally, on the recent Canadian Marijuana Survey, over half (55%) of Canadians 16 and older who reported using cannabis in the past 12 months felt cannabis had positive impacts on their mental health and quality of life, with 51% perceiving a positive effect specifically for mood and 50 % for anxiety (Government of Canada, 2017). Overall, medicalization and changes in the perceived benefit of cannabis suggests that the time-by-cannabis effect found in the current analysis may be reflective of a greater proportion of Canadians using cannabis for the purpose of self-medicating in 2012 compared to 2002. In other words, more individuals with pre-existing depression or suicidal behaviours may be using recreational cannabis to cope with their symptoms.

Summary of Temporal Contextual Hypotheses. This study found strong and consistent associations between monthly cannabis use and suicidal thoughts and attempts, MDE, and psychological distress in 2002 and 2012, with stronger associations in 2012. The nature of this study limits the ability to determine causality, but this discussion attempted to identify plausible mechanisms that may underlie the observed associations.

There are several debated hypotheses regarding the general association between mental illness and any substance use including: (a) individuals use substances to self-medicate or to cope with the symptoms of mental illness or stress, (b) substance use can worsen or cause symptoms of mental illness, (c) shared biological predispositions for both mental illness and substance use, and (d) there is a bidirectional relationship between psychological symptoms and substance misuse that leads to induction or an exacerbation of each other (Bolton, Robinson, & Sareen, 2009; Fergusson, Boden, & Horwood, 2011; Hathaway, 2003; Simantov, Schoen, & Klein, 2000). Despite the continued uncertainty in the nature of the association between cannabis use and emotional problems, what remains consistent is that cannabis use and emotional concerns are strongly related to one another. Therefore, regardless of causal pathways, when considering practice implications: exploration, assessment, and management of cannabis use should be a consideration in the context of emotional problems and vice versa.

Strengths and Limitations

This was a secondary analysis of two repeated population-based surveys. Due to the cross-sectional nature of the surveys, causality cannot be inferred, and therefore, the analyses focused on prevalence, the strength of associations, and population trends. The large data set poses the threat of revealing small statistically significant effects sizes, however, when interpreting results, clinically meaningful effect sizes and confidence intervals beyond statistically significant effects were considered. Importantly, the sampling design and use of weighting and bootstrapping enables population-based inferences, extending generalizability from the sample to the Canadian population.

By doing secondary analysis, sampling design and data collection have already been conducted. Despite saving time and resources, the data may not fully meet the needs of the present study. In the case of the present study, there were some discrepancies between the 2002 and 2012 surveys limiting comparability of several items (substance abuse and dependence, anxiety disorders, tobacco use). Therefore, the analysis was limited to variables that were measured similarly at both time points and sensitivity analyses were performed for the missing tobacco measure in 2002. Additionally, due to the data collection strategies, assessing for differences among responders and non-responders is impossible due to insufficient information of non-responders. This poses threats to validity, as total non-responders are typically different than responders. However weights were developed by Statistics Canada and applied to control for systematic differences.

As an observational study, there is a heightened risk of bias due to measured and unmeasured confounding. As described in detail in Chapter 2, step-wise multivariate regression was used to account for the potential confounding effects of key variables including other substance use and SES. The cross-sectional and temporal trends of the association between cannabis use and emotional problems remained even after controlling for other substance use and proxies of SES.

There are limitations with the conceptualization and measurement of our variables. All data were captured through self-report measures, which are prone to recall and social desirability bias. For example, substance use frequency measures are reliable (Flisher, Evans, Muller, & Lombard, 2004; Koning, 2010), although prone to underreporting and limited in their ability to determine fluctuations in use. Cannabis frequency items also did not capture age of onset, previous substance use problem, strain or composition of cannabis used, frequency of daily use, quantity of cannabis used, added tobacco (i.e. poppers), or method of delivery of cannabis product (i.e. smoke or ingested). Although there was a change in average composition of cannabis

over this period of time, the 10-year time period may not be long enough to pick up on average changes in chemical composition. Other secular changes have also occurred during this time period (e.g. increased electronic screen time, social isolation, reduced stigma in mental health, changes in mode of delivery of use etc.) that could represent an alternative explanation for any noted effects of this study that were not measured. Additionally, biological sex was measured by the interviewers judgment, and if necessary, the interviewer asked the participant if they were male or female, not indicating they were asking for biological sex as opposed to gender. Transgender or other gender identities were not available as response options and, individuals who identify as transgendered may not physically look like their biological sex and therefore, this may have resulted in errors during data collection (although this would be a small proportion of the sample

Both surveys were collected during the implementation of the Medical Marijuana Access Regulations allowing for people with certain conditions to obtain authorization to use cannabis for medical purposes. In the CCHS-MH 2002, participants were asked about their drug use, without specifying if it was used for medical or recreational purposes while in the CCHS-MH 2012, individuals are asked about nonmedical use. However, in 2003 only 605 Canadians were authorized for medical cannabis use therefore this difference in the operationalization of cannabis use does not pose a threat to validity of the analysis. It is also important to note that these analyses were done in the context of legal medical cannabis but illegal recreational cannabis. The current and impending changes in the social and political landscape of substance use in Canada will likely result in different patterns of behaviours within different groups trying and using cannabis. This will likely change the epidemiology, including both the distribution (who, when, where) and motivation for use and subsequent cannabis-related problems. Therefore, the associations found in this study may not be generalizable to the population after the national legalization of recreational cannabis.

Implications for Practice

Public Health Messaging. The results of this secondary analysis support existing recommendations in the Lower Risk Cannabis Use Guidelines (LRCUG) and suggest areas for stronger recommendations (Fischer et al., 2017). The LRCUGs recommend, that if individuals choose to use cannabis, they should limit their use, using at **most** once per week and caution against daily use. This secondary analysis found a dose-response association between frequency of cannabis use and emotional problems, with an increased likelihood of experiencing emotional problems even when individuals reported using rarely, or less than once a month. In the primary analyses, at least monthly use of cannabis was associated with a higher likelihood of

problems and this pattern was more strongly associated with emotional problems today than in the past. These results both support and call to question the current LRCUGs recommendations by supporting the warning that higher frequency use is associated with worse problems but questioning whether weekly cannabis use is an appropriate "low risk" recommendation. Based on overlapping confidence intervals for suicidal thoughts and attempts in this analysis, less than monthly use appears to be a more appropriate recommendation for minimal harm. The LRCUG also include statements that warn about the use of high THC products. Additionally, the odds of experiencing negative mental health outcomes increased during the same period in which the average THC increased in recreational cannabis in this analysis. Although this analysis was based on cross-sectional data, and it is unclear if the increased potency is driving the increased risk over time, the findings provide evidence for future inquiry into potency as a possible mechanism behind the increased odds between 2002 and 2012.

The findings of this literature review and secondary analysis provide further evidence to suggest that individuals who have pre-existing depression, anxiety, and suicidal thoughts or attempts should be prudent if deciding to use cannabis. This existing recommendation for individuals currently experiencing or at risk of depression and suicide should also indicate the need to closely monitor emotional symptoms if deciding to use cannabis, independently and with a health care or mental-health professional. In addition, there is an urgent need to differentiate recreational from medical use of cannabis. There are salient differences in the composition and delivery of medical compared to recreational cannabis (i.e. THC:CBD ratios), that may have differential associations with emotional problems. Especially due to the easy accessibility of medical cannabis and legalization of recreational cannabis, differentiating medical from recreational use is crucial due to the lack of existing evidence to support medical use of cannabis for emotional concerns and potential increases in the use of recreational cannabis for coping or self-medication purposes.

Current Best Practice. Best Practice Guidelines (BPGs) for depression in both children and adults acknowledge the bidirectional relationship between substance use and depressive symptoms. Both British Medical Journal (BMJ) Guidelines indicate the need to (MacKinnon, 2018; Pan & Brent, 2018): (a) determine if depressive symptoms are substance-induced prior to making a diagnosis or initiating psychopharmacological treatment; (b) regularly assess concurrent substance use alongside suicide risk, and (c) if an individual is not responding to treatment, re-evaluate and address potential comorbid substance use. A guideline for suicide risk assessment also recommends assessing the presence of comorbid substance use as a risk factor for increased risk of suicidal thoughts and behaviours, noting that

depression and substance use are the most prevalent disorders associated with suicide risk (Kutcher, 2018).

The Canadian Centre on Substance Abuse (2009) indicated a need for improved care and treatment of concurrent mood and substance use disorders including improving detection, diagnosis, and concurrent treatment of (or awareness of) both disorders. This document acknowledged a lack of evidence regarding treatment options and best practices for concurrent disorders, although stated that treating both problems simultaneously is preferential to treating them separately. The National Institute on Drug Abuse (2018) indicates that psychotherapy, such as cognitive behavioural therapy (CBT), contingency management, and motivational enhancement therapy (MET) have shown promise in treating cannabis-related problems. UpToDate, a summary clinical text, also recommends CBT along with MET as first line therapy for cannabis use disorder (although indicates this is a weak recommendation) (Gorelick, Saxon, & Hermann, 2018). CBT is also suggested as the first line psychotherapy treatment for depression (MacKinnon, 2018; Pan & Brent, 2018; Simon, Roy-Byrne, & Solomon, 2018). Additionally, evidence suggests that reductions in cannabis use are associated with concurrent depressive symptom improvement (Moitra, Anderson, & Stein, 2016). A general consensus across existing BPGs suggests, if an individual is presenting with one of the two issues (i.e. mental health or substance use), they should be assessed, monitored, and treated for concurrent issues at all phases of diagnosis, treatment, and monitoring. Although research on treatment of concurrent disorders is limited, it is also important to note that CBT is indicated for the treatment of both depression and cannabis-related problems, and may therefore be an ideal treatment option for individuals presenting with both problems until further research is done.

Brief interventions are also commonly used to provide health education to patients about their substance use non-judgmentally, promote motivation to change substance use behaviours, and facilitate referrals and follow-up care (Bien, Miller, & Tonigan, 1993; Matua Raki, 2012; NIDA, 2012; World Health Organization, 2010). Brief interventions are commonly only 1-2 sessions and typically range between 5 to 90 minutes in length. Most brief interventions are grounded in motivational interviewing or enhancement (Bien et al., 1993; Matua Raki, 2012; NIDA, 2012; World Health Organization, 2010). The National Institute on Drug Abuse provides a structure of brief interventions for clinicians: Advise, Assess, Assist, and Arrange (NIDA, 2012). Within this structure, a clinician would provide medical advice about the patient's specific drug use, assess the patients readiness to change their substance use behaviours, assist them in making a change, and arrange follow-up or referrals. Other organizations, including the World Health Organization, suggest the FRAMES model, which includes providing personalized feedback, discussing the individuals'

personal responsibility and asking permission to provide feedback or advice, providing objective advice non-judgmentally, having a menu of options, being empathetic and accepting, and encouraging self-efficacy and confidence (Bien et al., 1993; Matua Raki, 2012; World Health Organization, 2010). There is evidence that brief interventions are effective for reducing alcohol use and related harms (Álvarez-Bueno, Rodríguez-Martín, García-Ortiz, Gómez-Marcos, & Martínez-Vizcaíno, 2015; Tanner-Smith & Lipsey, 2015) but there is insufficient evidence for the effectiveness for illicit substances (Young et al., 2014). No systematic reviews have currently been conducted on the effectiveness of brief interventions (defined as 1-2 sessions) for cannabis use, however, as stated previously, MET has shown promise in treating cannabis disorder, and brief interventions fall under the umbrella of MET-related interventions (Gorelick et al., 2018). There is insufficient evidence for brief interventions to be included in BPG recommendations for cannabis use. However, the effectiveness of brief interventions for alcohol, the theoretical underpinnings related to MET, and minimal resources (time and money) required to implement brief interventions suggest this approach may be a promising treatment modality for cannabis use.

Monitoring for Substance Use Concerns. Clinicians should carefully monitor substance use among all patients, regardless of developmental age, both within and outside the context of emotional problems. Pre-existing BMJ Best Practice Guidelines (BPGs) for depression care among youth and adults suggest evaluating comorbid substance use prior to diagnosing depression, during the course of treatment of depression, and especially so if an individual is not responding to conventional treatment or relapses (MacKinnon, 2018; Pan & Brent, 2018). Additionally, UpToDate (Kelly, Drutz, & Torchia, 2018) synthesizing recommendations from The American Academy of Pediatrics and Bright Futures (Bright Futures/American Academy of Pediatrics, 2017) and The American Academy of Family Physicians (American Academy of Family Physicians, 2017) suggest annual general screening for alcohol use beginning as early as 9 years of age, and tobacco and other substance use beginning at 11 years of age. UpToDate recommends using the CRAFFT (Center for Adolescent Substance Abuse Research, 2009) for general substance use among youth. A recent rapid synthesis (Hartman, 2017) found 25 validated screening and assessment tools specifically for cannabis use, with the best performing tools being: the Cannabis Use Disorders Identification Test (Adamson et al., 2010), Cannabis Abuse Screening Test (Legleye, Karila, Beck, & Reynaud, 2007), Drug Use Disorder Identification Test (Berman, Bergman, Palmstierna, & Schlyter, 2005), and Alcohol, Smoking, and Substance Involvement Screening Test (WHO ASSIST Working Group, 2002). Despite these recommendations, there is currently limited evidence on the benefits and harms of screening, particularly among adolescents and for substances other than alcohol (Moyer, 2013; Patnode et al., 2014).

The lack of reporting on the harms of screening is not unique to mental health and substance use concerns. In response to this gap in the literature, Harris et al. (2014) proposed a taxonomy of the harms of screening to assist future research. Harris et al. (2014) proposed four domains of harm including physical harms, psychological harms, financial strain, and opportunity costs. Potential physical harms of cannabis screening could include paradoxical effects of the screening and/or brief intervention leading to more substance use and other risky behaviours, including self-harm or suicide attempts. Psychological harms could include anxiety or distress, feeling stigmatized, or detrimental impacts on the therapeutic relationship. Financial strain may result from the cost of training and implementing screening and follow-up procedures. Opportunity costs may result from wasting time on screening and brief interventions as opposed to other more impactful interventions. All of these harms could be further compounded by misclassification and unnecessary treatment as a result of screening. These harms are speculative, and existing evidence does not provide support for these harms but there is insufficient evidence to make clear recommendations at this time (US Preventive Services Task Force, 2014).

The existing general recommendations for substance use monitoring, although based on limited evidence, include:

1. Targeted monitoring and screening of mental health problems if presenting with substance use problems and vice versa (particularly psychosis, anxiety, and depression if presenting with cannabis use)
2. Targeted monitoring and screening of mental health or substance use concerns if presenting with other risk factors, such as changes in functioning, academic or occupational performance, or recent psychosocial stressors
3. Universal screening at least annually for substance use problems (beginning at 12 years of age) and follow-up plan for those identified through screening.

In addition to the frequency of screening, when deciding to screen, clinicians need to determine what screening tool to use (i.e. self-report or urine drug screens), who will be administering the tool (i.e. nurses, automatic at check-in, physician), and how the results will be used (i.e. health teaching, brief intervention [e.g. motivational interviewing], full assessment, psychotherapy [e.g. CBT] and/or follow-up) (National Institute on Drug Abuse, 2010).

Future Research

This secondary analysis met several of the research targets identified in the National Research Agenda on the use of Non-Medical Marijuana Use (Canadian Centre on Substance Abuse, 2017). This agenda stated the importance of providing baseline data on the Canadian population prior to the legalization of recreational cannabis use. This study provides national baseline data on the associations between current recreational cannabis use and emotional problems, and how this relationship has changed over time (particularly during medical legalization). The CCSA also prioritized understanding individual characteristics associated with differences in associated harms. This secondary analysis revealed that the increased association between cannabis use and emotional problems was consistent across developmental ages and biological sexes, suggesting a universal increased risk over time. The CCSA also prioritized exploring polysubstance use and how cannabis affects the brain when used in combination with other substances. This secondary analysis provides evidence to support that cannabis use is associated with emotional problems over and above other substance use, and appears to have the largest substance related contribution to the variance in emotional problems in the Canadian population.

Moving forward, Canadians who choose to use cannabis once it is legalized may have different characteristics to those who have chosen to use in the past. Therefore, the prevalence and patterns of use and the risk and protective factors for subsequent cannabis-related problems may change following legalization. Therefore, the existing evidence should be used as baseline information to inform initial strategies for public health, monitoring, treatment and to inform future research.

With this in mind, future epidemiological and population based research should learn from the salient limitations of existing epidemiological surveys and ensure future studies capture: (a) the strain and potency of cannabis being used (this will be provided for legal cannabis); (b) the frequency of days used, number of times in a day and the amount used (grams); (c) method of delivery of use (i.e. vaporizing, edibles, smoking); and (d) motives for using and if individuals are using alone or with others. Epidemiological studies on cannabis use should also include measures of mental health (primarily signs of psychosis, depression, anxiety, and suicidal thoughts and attempts) and other substance use (including chronic and acute alcohol use, tobacco use, and other illicit substance use). If possible, longitudinal studies should be conducted to determine the sequencing of substance use (i.e. gateway) and mental health problems (i.e. to determine the direction of the relationship between mental health and substance use). Additionally, the role of SES in the relationship between cannabis use and emotional problems needs to be appropriately explored, which requires development of tools that adequately operationalize and measure SES across

the life course. Future studies need to explore the psychometric properties and utility of measures such as subjective financial status and social status across developmental periods, and integrate such measures into population-based surveys. Lastly, the CCHS-MH component (or the same modules for MDE, suicide, and cannabis use) should be repeated near the beginning of legalization and several years later in order to compare between the beginning and later stages of medical cannabis legalization and the beginning and later stages of recreational cannabis legalization in the Canadian population.

There is a paucity of clinical practice-related research on the screening, monitoring, and treatment of cannabis use and concurrent cannabis and mental health problems. It is pertinent to conduct research focused on the benefits and harms of screening for emotional and substance use problems in primary care. Further research on brief interventions, specifically for cannabis use, is also required. Additionally, further research needs to be done on the treatment of concurrent disorders, particularly the effect of simultaneous or stepped treatment of cannabis use and emotional problems. The existing evidence is limited and focuses more broadly on the co-occurrence of any substance use disorder and other mental health disorder. Due to the high prevalence of both cannabis use and emotional concerns, and the strong associations between these phenomena, interventions should be designed and evaluated to target both simultaneously.

It is also important to examine the potential clinical benefits of cannabis for emotional problems, particularly CBD predominant strains or oils. Given the use of cannabis for coping purposes and the public perception that cannabis is beneficial for mental health, evidence supporting or refuting these beliefs is urgently needed. There is little current evidence supporting the use of cannabis for emotional problems, though studies are currently investigating the potential benefits of CBD in anxiety in particular.

Lastly, policies related to medical cannabis may need to be re-evaluated. There is a need for improved oversight of medical cannabis to avoid the use of medical cannabis for recreational purposes and use for conditions with little to no evidence especially when there is potential for harm. Canada requires monitoring of cannabis prescribing, especially for mental health-related conditions. This monitoring could include alternative treatments attempted prior to prescribing (i.e. other first and second line psycho-pharmacotherapies and psychotherapies), and the strain, potency, amount, and method of delivery of cannabis prescribed. Research focused on individuals using medicinal cannabis should explore both the short and long-term clinical effects and side effects related to use.

Conclusion

In conclusion, any cannabis use was consistently related to depression, psychological distress, and suicide in a dose-response fashion and was more strongly related to these problems in 2012 than in 2002. Although the cross-sectional design inhibits the ability to determine the causal pathway between cannabis use and emotional problems, there is no existing epidemiological evidence to suggest that recreational cannabis is helpful or beneficial for emotional problems. The findings of this study provide a baseline for the association between cannabis use and emotional problems in the Canadian population prior to recreational legalization.

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