Examining the association between affective disorders with psychotic features and cannabis use 30 days prior to admission to inpatient psychiatry in Ontario, Canada, from 2016-2019

by

Tatung Nath

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Author’s Declaration

I hereby declare that I am the sole author of this thesis. This is a true copy of the thesis, including any required final revisions, as accepted by my examiners.

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Abstract

Background: Cannabis use is associated with the risk of developing psychosis. There is substantial research on the association between cannabis use and non-affective psychotic disorders, but few studies have examined the relationship between cannabis and affective disorder with psychotic features (ADPF). **Objectives**: To investigate the association between ADPF and cannabis use 30 days prior to admission to inpatient psychiatry and to explore the role of age and gender as effect modifiers. **Methods**: Data from the Ontario Mental Health Reporting System collected between 2016-2019 were used to conduct multivariable regression analyses. Binary logistic regression analyses were performed to investigate whether the odds of having used cannabis were greater among those with ADPF compared to those without ADPF and whether the association was moderated by age or gender. **Results**: Among those with affective disorders, those with psychotic features were at no greater odds of having used cannabis 30 days prior to inpatient psychiatric admission compared to those without psychotic features. Gender was found to modify the association between ADPF and cannabis exposure. Being female with ADPF was associated with lower odds of using cannabis prior to inpatient psychiatric admission than females without ADPF. Compared to males without ADPF, males with ADPF were at no greater odds of having used cannabis within 30 days prior to admission. Overall, a larger proportion of males used cannabis prior to admission, compared to females. Age was not found to modify the association between ADPF and cannabis exposure. **Conclusion**: In addressing gaps in the literature regarding cannabis use and affective psychotic disorders, the results of the study demonstrated a nuanced gender-based relationship between ADPF and cannabis use. Based on these findings, the study has implications for informing early intervention initiatives for harm reduction and clinical practice among persons with severe mental health concerns.

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List of Abbreviations

THC	Δ9-tetrahydrocannabinol
CBD	Cannabidiol
ECS	Endocannabinoid system
ECB	Endocannabinoid
2-AG	2-arachidonylglycerol
CB1/CB2	Cannabinoid Receptor Type 1/2
AD	Affective Disorder
ADPF	Affective disorder with psychotic features
MDD	Major depressive disorder
BD	Bipolar disorder
OMHRS	Ontario Mental Health Reporting System
CIHI	Canadian Institute for Health Information
RAI-MH	Resident Assessment Instrument-Mental Health
PSS	Positive Symptom Scale
OR	Odds ratio
CI	Confidence interval
CUD	Cannabis use disorder

1. Background

Cannabis is one of the most commonly-used drug in the world, with 192 million users reporting past-year use (1). Cannabis use in North America, Africa and Asia has increased since 2009. The highest prevalence of use is reported in North America at 14.6%, compared to 10.6% in Australia and New Zealand and 9.3% in West and Central Africa (1). Adolescents and young adults, in particular, are at the highest risk of cannabis use around the world (1). With this widespread use, it is important to monitor the impact of cannabis use on public health to reduce harm to populations that are vulnerable to experiencing adverse effects.

1.1 What is cannabis?

Cannabinoids are found in plants, called phytocannabinoids, in synthetic cannabinoids and in the human body (i.e. endocannabinoids). Cannabis originates from Central and Northeast Asia, where it has been used for over 5000 years for therapeutic, spiritual and recreational uses(1,2). Cannabis sativa, or cannabis, is a phytocannabinoid-containing plant from which 483 known compounds have been identified, 70 of which are cannabinoids. Δ9-tetrahydrocannabinol (THC) is the main psychoactive cannabinoid that is found at the highest proportions out of all other cannabinoids contained in cannabis.(2) Cannabidiol (CBD) is another main cannabinoid known for its anxiolytic effects.(3)

1.2 Forms and Potency:

In North America, cannabis is available in forms, such as dried herb, concentrates, topical ointments, oils, tinctures and beverages.(4) The most commonly used cannabis products in Canada are dried herb/flower, edibles, vape pens or cartridges, hashish or kief, orally-administered cannabis oil, and concentrates or extracts.(5) With the increasing availability and legalization of cannabis products, the potency of THC in cannabis has been increasing over time worldwide.(6) According to ElSohly et al.(7), the content of THC in cannabis products in the US has increased from 14 to 80 times greater than CBD content between 1995 to 2014. The concentration of THC has increased from approximately 4% in 1995 to approximately 12% in 2014, while the concentration of CBD has decreased, on average, from approximately 0.28% to <0.15% between 2001 to 2014.(7) Similar trends have been reported in European countries where herbal and resin-type cannabis have increased in THC content between 2006 to 2016.(8) Hash oil tends to have more than 50% THC, hashish contains 20% THC, and herbal cannabis (resin) has 5% potency of THC.(6) The ratio of THC:CBD has increased in The Netherlands, United Kingdom, France, and Italy from 2008 to 2017 where THC content is greater by 23 to 104 times than CBD.(9) In Canada, the

concentration of THC is found to be 20.5% and 16.1% for illegal and legal cannabis, respectively. Whereas the levels of CBD are found to be 2.4% and 1.7% for illegal and legal cannabis, respectively.(10) High-potency cannabis is a concern as it puts the public at a greater risk of experiencing various adverse effects associated with frequent use.

1.3 Effects and Uses:

Cannabis use is associated with various short- and long-term adverse effects. Short-term adverse effects include impairments in memory, motor coordination, altered judgement, paranoia and psychosis. These adverse experiences are associated with the use of high-potency cannabis, in particular. Long-term regular use (e.g. daily use) is associated with cannabis dependence, chronic bronchitis symptoms linked to smoking herb type cannabis, and an increased risk of the onset of psychotic disorders. Initiation of heavy and long-term cannabis use during adolescence affects brain development and is linked to cognitive impairment and feelings of lower life satisfaction and achievement.(11)

Despite the potential risks of cannabis use, individuals report using cannabis for a variety of recreational and therapeutic reasons. It is commonly used to relieve pain, anxiety and sleep disturbances.(12) Young adults report using it to conform with their peer group, socialize, self-medicate, engage in experimentation, relax, and alleviate feelings of boredom.(13,14) Amongst persons with severe mental illness, Gill et al.(15) found that individuals with psychosis report using cannabis as a means of self-medication for alleviating psychotic symptoms or anxiety. Interestingly, among individuals with schizophrenia, cannabis is used as a means of socialization and to elevate mood as a means to alleviate symptoms of anhedonia.(15,16)

Some of the effects of cannabis have biological origins in the human body, particularly in relation to the implications of psychosis. Research on the effects of THC on human biology has focused on three components: endocannabinoids (ECB), cannabinoid receptors, and enzymes.(17) This endocannabinoid system (ECS) is involved in modulating pain perception, cognition and memory.(18) There are two ECB receptors of importance, cannabinoid receptor type-1 (CBR1) and cannabinoid receptor type-2 (CBR2).(18,19) They act as mediators of the effect of cannabis on the central nervous system.(19) CB1 receptors, along with the ECS, are implicated in the development of schizophrenia and addiction, in addition to other mental health conditions such as anxiety and depression.(19) Essentially, chronic exposure to cannabinoids introduced from the consumption of cannabis can disrupt the body's normal functioning of CBR1 and CBR2 (e.g., retrograde signaling (20)) that maintain homeostasis in the body(20), affecting

emotions, cognition, memory, and reward systems.(21) Interestingly, CB1R availability may be reversible over the course of a few weeks after cannabis cessation.(22,23) The role of phytocannabinoids in relation to the development of psychosis through the ECS is an ongoing area of research.

1.4 Cannabis Use and Mental Health in the Canadian Context:

There has been an increasing trend in cannabis use in Canada across age groups and sexes. Between 2004-2017, cannabis use in the past year in Canadian households increased from 9% to 14%. Interestingly, rates of use have increased among 24-64-year-olds, decreased among 15-17-year-olds and have remained stable among 18-24-year-olds.(15) After legalization in 2018, the prevalence of cannabis use increased from 14% to 18%, with 5.3 million Canadians reporting using cannabis in the three months post-legalization. Use increased significantly among males, from 16% in 2018 to 22% during the first quarter of 2019.(15)

In Canada, the overall rate of hospitalizations related to mental health conditions among cannabis users nearly doubled from 525 to 1430 between 2006 and 2015 (2.11 to 5.18 per 100 000).(16) The majority of those who were hospitalized were male (70%), and 49-58% of hospitalizations were attributed to youth aged 15-24 compared to all other age groups. Alarmingly, youth hospitalization rates have increased by 19 times since 2006. Rising trends in cannabis-related hospitalizations associated with psychotic disorders are of major concern, as well. It was the most common clinical condition out of all mental health conditions for which patients were hospitalized between 2006-2015. Hospitalizations for cannabis-related psychotic disorders have tripled from 0.80 to 2.49 per 100 000.(16) Use of cannabis prior to inpatient psychiatry admissions has also increased substantially between 2007 and 2017, with almost 50% of patients reporting cannabis use prior to the first admission in 2017, representing a 10% increase over 10 years.(24) There are a number of possible explanations suggested by Canadian researchers for the increase in hospitalizations, including increasing availability of high-potency cannabis containing high levels of THC, a changing public sentiment related to the benefits of cannabis, and changes to how clinical settings collect information about cannabis.(16,24)

1.5 What is psychosis and what are psychotic disorders?

Psychosis is characterized by positive, negative, affective, and cognitive symptoms. Positive symptoms include delusions, hallucinations, and difficulties in thinking, speech, or behaviour, while negative symptoms include anhedonia, loss of motivation, withdrawal, and disruptions in speech and verbal

fluency.(25) Psychosis is commonly known as a symptom of schizophrenia in addition to other psychotic disorders such as, schizophreniform disorder, schizoaffective disorder, major depression with psychotic features, drug-induced psychosis, organic psychosis, brief psychotic disorder, delusional disorder and bipolar disorder with psychotic features.(25)

1.6 Risk Factors of Psychosis, Schizophrenia and Psychotic Disorders:

Neurobiological and other risk factors affect the onset and severity of psychotic symptoms including, altered synaptogenesis, altered synaptic pruning, disrupted excitatory/inhibitory balance, loss of gray matter, and dopamine dysfunction.(26) Other risk factors include genetic factors, prenatal complications, childhood trauma, urbanicity, ethnicity, stress, patterns of substance use (especially cannabis use), and treatment adherence.(26) Genetics risk factors contribute strongly to the risk of developing schizophrenia-spectrum disorders. Family history is strongly associated with a greater risk of onset of schizophrenia. Heritability estimates for schizophrenia range from approximately between 64-81% (27–29), where variations in the risk of developing schizophrenia can be explained largely due to genetics.(30)

There are various socioenvironmental factors associated with an increased risk of experiencing psychosis. Prenatal and perinatal risk factors include famine or nutritional deprivation and obstetric complications.(31,32) In 2017, Fusar-Poli et al.(13) conducted a meta-analysis and systematic review of 44 studies with 54 risk factors for being “ultra high-risk” for developing psychosis. Ultra high-risk groups consist of those who are genetically vulnerable to developing psychosis, or have a history of experiencing positive psychotic symptoms within the past year (i.e. history of Attenuated Psychotic Symptoms), or have a history of exhibiting early signs of psychotic symptoms lasting for a duration of less than one week (i.e. history of Brief Limited Intermittent Psychotic Symptoms.(13,33) The study found that risk factors for those at ultra-high risk of psychosis include, physical inactivity, use of tobacco, male gender, single status, high perceived stress, affective comorbidities and unemployment/low education attainment.(13) Aside from obstetric complications, other childhood risk factors include childhood trauma/emotional abuse/physical neglect, high perceived stress, and low functioning during childhood/adolescence. Interestingly, cannabis exposure was not associated with being high risk due to potential confounding with alcohol use, according to Fusar-Poli et al.(13) However, findings from another meta-analysis show that cannabis use is prevalent and is associated with greater severity of psychotic symptoms among those at ultra high-risk.(34)

1.7 Cannabis Use, Psychosis, Schizophrenia and Other Psychotic Disorders

There is substantial research examining the risk factors and onset of psychosis. Evidence suggests that cannabis use may exacerbate psychotic and other symptoms of schizophrenia and is linked to earlier onset of psychosis.(35) D'Souza et al.(36) suggest that cannabis use is likely a component cause for the onset of psychosis among vulnerable individuals. A meta-analysis on the association between cannabis use and the risk of developing psychosis demonstrated that the odds of schizophrenia and other psychosis-related outcomes were 3.90 higher among heavy cannabis users than non-users.(37) Another notable case-control study among individuals using high potency cannabis showed that the odds of developing psychotic disorder was approximately 3 times higher among cannabis users vs non-users. Furthermore, the odds of psychotic disorder were 5.4 times higher among daily users compared to never users.(38) Di Forti et al.(39) found that high potency users experienced an earlier age of onset of psychosis by approximately 3-4 years (mean age=26.7 years vs 30.1 years for high and low-potency users, respectively) compared to low-potency users. Other studies have reported similar findings on early onset of psychosis and psychotic disorders, especially among men.(40–42). Di Forti et al.'s(43) multi-centre case-control study in Europe, for example, demonstrated that the odds of psychotic disorder was highest among those who used cannabis on a daily basis compared to those who never used cannabis (adjusted OR: 3.2, 95% CI 2.2-4.1). Daily users of cannabis products with the highest potency had an adjusted 4.8 greater odds of psychotic disorder onset than never-users. In other words, the odds of psychotic disorder onset were almost five times greater among high potency daily cannabis users and approximately 3 times greater among daily users compared to never users. These findings not only suggest that potency and frequency of use account for some of the variation observed in the incidence of psychotic disorders, but they also indicate that there is evidence for the presence of a dose-response effect. These findings not only suggest the presence of a potential dose-response where frequent use of high-potency cannabis products is associated with higher odds of onset of psychotic disorder, but they also indicate that frequent use at a younger age is associated with increased risk of psychotic disorder.

Understanding how cannabis directly relates to the risk of psychosis is complex. For instance, adverse childhood events have been found to be associated with the development of schizophrenia and future substance use disorders.(44–46) Similarly, cigarette smoking is correlated with later cannabis use and schizophrenia.(46). Genetic studies have attempted to examine the causality between cannabis use and psychotic disorders. For example, Karcher et al.(47) conducted a cross-sectional twin study and found that concurrent cannabis use, cannabis use disorder (CUD) and frequent cannabis use was associated with an

increased risk of psychotic-like experiences.(47) Cannabis users were at least 1.21-1.26 times at greater risk of experiencing at least 1 psychotic-like experience compared to those who used cannabis infrequently or never at all. Furthermore, genetic polymorphisms in relation to cannabis use such as, BDNF Val66Met and COMT Val66Met, are an ongoing area of study with regard to the genetic links to psychosis. Evidence is conflicting. Some report that genetic polymorphisms such as BDNF Val66Met are associated with earlier onset of psychosis, although the associations are weak, and no correlation was found for COMT Val66Met.(42,48) Mané et al.(48) found that early initiation of cannabis use was significantly associated with earlier onset of psychosis among cannabis users with BDNF Val66Met polymorphism and among males. Differences in age at psychosis onset were observed among female met-allele carriers; however, further research is needed to gain an understanding of the biological mechanisms at play.

There is an ongoing debate about the causal association between cannabis and psychosis within the field of genetics. Vaucher et al.(49) used Mendelian randomization and meta-analytical methodologies examining genetic and socio-environmental factors in teasing out the association between cannabis and psychosis, finding a strong association between cannabis and psychosis. They suggested that a causal relationship is a "strong possibility" given that the markers of cannabis use were strongly associated with psychosis holding all other genetic and socioenvironmental factors constant. Gage et al.'s(50) Mendelian randomization study also found greater odds of developing schizophrenia among cannabis users. However, the study found a stronger association between initiation of use among those predisposed to schizophrenia, suggesting that there are both social and genetic mechanisms at play. Results from Pasman et al.(51) had similar findings to Gage et al.'s(50), where the gene, CADM2, was found to have a stronger association with lifetime cannabis use among individuals with schizophrenia and a weaker association in the opposite direction.

1.8 Affective Disorders:

1.8.1 Major Depressive Disorder and Cannabis Use:

Major depressive disorder (MDD) is a mental disorder characterized by low mood lasting two or more weeks. Specific characteristics of MDD include a mixture of physical and psychological effects such as changes in sleeping patterns, loss of appetite, anhedonia, suicidal thoughts, crying, constipation, and decreased sexual desire.(52) The lifetime prevalence of MDD is approximately 10% in the United States and 11% in Canada.(53,54) The mean age of onset averages around 29 years of age.(54) MDD is more prevalent in women compared to men.(54,55)

The rates of cannabis use have increased among those with MDD over time. Between 2005-2016 in the United States, the odds of past-month cannabis use were 1.90 times greater for those with MDD compared to those without MDD. Similarly, the odds of near-daily use were 2.29 times greater among those with MDD compared to those without depression.(56) Findings from a cross-sectional survey among Canadian adults demonstrated a stronger association between past-month cannabis use and depression in 2012 compared to 2002. The increase in the strength of the association suggests that there has been a change in risk perception and potency of cannabis over time.(57)

Although cannabis use is common among those with MDD, the directionality of association is unclear, and the underlying biological mechanisms for establishing causality require further research. Lev-Ran et al.' s(58) review of 14 longitudinal studies found that the likelihood of developing depression was 1.62 times greater among heavy cannabis users, compared to non-users and light users.

On the other hand, findings from other literature have reported that the onset of MDD in adulthood was associated with a decreasing level of cannabis use over time.(59,60) Some literature has also suggested(61–63) that there is a lack of association between cannabis use and the onset of MDD. (61–63) While Feigngold et al.(63) found that cannabis use was not associated with later onset of MDD at 3 year follow up, having MDD was associated with cannabis use. The association between cannabis use and subsequent onset of severe MDD is confounded by sociodemographic and clinical factors.(63) Further prospective longitudinal studies are required to parse whether the association is bidirectional and whether a dose-response relationship is present.

The variations in associations between cannabis use and MDD suggest the potential presence of a more nuanced link. Scholeler et al.'s(59) study found that initiation of use during adolescence (for males less than 18 years old) compared to initiation during adulthood was associated with MDD later in mid-life. However, initiation during adulthood was not associated with the onset of MDD in mid-life, and others have found similar results.(64,65) This suggests that vulnerability to adverse effects can vary by age, especially in adolescence, a developmental period with high vulnerability to the adverse effects of cannabis use.(66) In relation to gender-based differences, males with depression have been reported as 2.2 times more likely than females with depression to have a comorbid CUD.(67) Further research is required to understand reasons for cannabis use at a younger age, as many report use to cope with anxiety and depression.(12,68)

Research on the potential underlying mechanisms at play is unclear. Emerging evidence suggests that continued cannabis use is associated with poorer mental health outcomes. Bahorik et al.'s(69) study found that outpatients using cannabis within a month prior to assessment at baseline exhibited more severe symptoms of depression and anxiety and overall poorer mental health and functioning over the course of 3-6 months. In a longitudinal study, reductions in cannabis use have been shown to reduce anxiety and depressive symptoms and improve quality of sleep.(70,71) These findings suggest that cannabis use is an important consideration in treatment planning among individuals reporting depressive symptoms and those with a diagnosis of MDD.

1.8.2 Bipolar Disorder and Cannabis Use:

Bipolar disorder (BD) is a mental illness that consists of drastic mood swings shifting between depressive and manic episodes. It can be a debilitating condition if left untreated. The lifetime prevalence of BD worldwide is found to be approximately 2%.(72) In the DSM-5, the subtypes of bipolar disorder include bipolar I, bipolar II and cyclothymic disorder. Bipolar-like symptoms similar that do not meet the criteria for the diagnosis of bipolar I, II or cyclothymic disorder can be classified into the "other specified bipolar and related disorders" category.(73) In Canada, the estimated prevalence is approximately 0.87% for BD I and 0.57% for BD II, in the general population.(74) In inpatient populations, the rates of comorbid CUD have been estimated to be much greater compared to the general population, with 39% of people with BD being having CUD compared to approximately 16% in community-based samples.(75) In terms of variations by sex and age, the distribution of BD is reported to be roughly equal between males and females. Individuals may experience the onset of BD at various life stages, with a majority occurring during early life (ages 14-21 years). The age of onset of BD is found to be 17.5 years on average, with 45% of cases occurring in early life between 14 to 21 years. The rest occur largely during mid-life between 20s and 30s and late-life onset among those over 45 years old.(76)

Cannabis use is common among people with BD and can differ by demographic characteristics such as age and gender. One meta-analysis(77) found that every 1 in 4 individuals with BD was found to be cannabis users, and it is more prevalent among individuals with BD compared to those with MDD.(78) BD has also been associated with several clinical and demographic characteristics. Males with BD are more likely than females to use cannabis, most commonly used among younger age groups and people with fewer years of education.(77) Findings from Kozak et al.'s(67) systematic review and meta-analysis demonstrated that males with BD were 1.7 times more likely to have a comorbid CUD compared to females with BD.

In terms of clinical outcomes, cannabis use is associated with a worse course of illness among those with BD. It is linked with a greater risk of suicide attempts, other substance use (e.g. tobacco, alcohol and other substances), and earlier age of onset of affective and psychotic symptoms compared to non-users.(77) Comorbid CUD among those with BD I has similarly been found to be associated with being younger, experiencing manic/mixed episodes, psychotic features, other substance use and substance use disorders.(79) In a meta-analysis of 11 studies, predominantly consisting of cross-sectional studies, found that suicide attempts were associated with comorbid CUD among those with BD.(80) Additionally, cannabis use is a potential risk factor for the first onset of manic symptoms and can impact the course of illness of those who continue to use it with a diagnosis of BD, as continued cannabis use can worsen symptoms of mania.(81) Continued cannabis use lowers the likelihood of improving clinical (e.g. manic and depressive symptoms remission) and functional health outcomes compared to individuals with BD who do not use cannabis.(82,83) Another study among tobacco consumers found that having CUD increased the likelihood of experiencing the earlier onset of BD, manic episodes, and being hospitalized.(84)

Jefsen et al.'s(85) Mendelian randomization study found evidence of a potential causal effect on the risk of using cannabis among those with BD. However, there was no evidence to suggest a causal effect of developing BD from cannabis use. Further research is required to investigate the underlying mechanisms at play in the relationship between cannabis use and bipolar disorders to delineate evidence for causality further.

1.8.3 Cannabis Use and Affective Psychotic Disorders:

Affective psychotic disorders include major depressive disorder (MDD) with psychotic features or psychotic depression and bipolar disorder (BD) with psychotic features or psychotic bipolar disorder. The prevalence estimates are generally found to be low. Studies have examined the lifetime prevalence of affective psychotic disorders among sampled populations based on population-based surveys using DSM III and DSM IV criteria. One study (86) estimated the lifetime prevalence of MDD with psychotic features to be 0.35% among those with affective psychotic disorders, which included BD with/without psychotic features. In a population-based study of 5 European countries, the point prevalence of DSM IV MDD with psychotic features was 0.4% out of the general population.(87) Findings from Jääskeläinen et al.'s(88) systematic review of 43 studies demonstrated that the median proportion of psychotic depression was 28% among samples with depression. The proportions of psychotic depression were found to be greater among inpatient psychiatric patients. In terms of gender, a greater proportion of females (65%) than males were

found to have psychotic depression. The age of onset of psychotic depression did not significantly differ from those with non-psychotic depression.

Among those with BD, it is common to have experienced psychotic symptoms. Van Bergen et al.'s(89) cross-sectional study among 1342 participants found that 73.8% of those with bipolar disorder I had a lifetime history of psychotic symptoms, and those with psychotic symptoms experienced an earlier onset of bipolar disorder. Another reported similar findings where individuals with BD with psychotic symptoms experienced earlier onset of BD compared to those with BD without psychotic symptoms, and over half (57%) of the sample had a lifetime history of psychotic symptoms. Individuals with psychotic symptoms were also found to have higher rates of comorbid alcohol or substance use disorder and overall worse clinical outcomes.(90)

Research on the impact of cannabis use on affective psychotic disorders is sparse but emerging. The majority of studies examining the association between cannabis and AD focus on BD, but few examine specific associations with psychotic features. Several studies have found that the use of cannabis is associated with an exacerbation of manic and psychotic symptoms among those with bipolar disorders.(81,91) Among individuals with bipolar disorder, persons with a co-occurring CUD or reported use of cannabis were more likely to present with lifetime psychotic symptoms and earlier onset of psychotic episodes.(77,92) One study reported a greater likelihood of delusional beliefs among persons diagnosed with cannabis misuse among individuals with bipolar disorder I.(93) Another study consisting of Swedish military men did not find a statistically significant association between cannabis use and the diagnosis of affective psychosis and BD diagnoses combined as one indicator.(94) The impact of cannabis on MDD, especially among those presenting with psychotic features, remains inconclusive.(91) Mustonen et al.'s(94) study conducted among adolescents found a statistically significant association between lifetime cannabis use and psychotic depression. However, limitations of studies so far must be kept in mind, such as heterogeneity of samples, varied measures of cannabis use (often lifetime or ever use) and lack of prospective study designs. Ultimately, little evidence is available on the association between cannabis use and the experience of psychotic symptoms of affective disorders (AD), which calls for a need for future research on the topic.

2. Study Objectives:

The study will examine the association between affective disorder with psychotic features and the use of cannabis within 30 days of admission to inpatient psychiatry between 2016 and 2019 in Ontario, Canada, compared to those without a diagnosis of affective disorder with psychotic features. This objective will be explored through the following research questions:

Research question 1: Among adults with affective disorders admitted to inpatient psychiatry in Ontario between 2016 and 2019, are those with affective disorder with psychotic features at greater odds of having used cannabis 30 days prior to admission compared to patients with affective disorder without psychotic features?

Furthermore, age and gender will be considered as effect modifiers as follows:

Research question 1a: Does age modify the odds of having used cannabis 30 days prior to admission among patients with affective disorder with psychotic features compared to patients with affective disorder without psychotic features?

Research question 1b: Does gender modify the odds of having used cannabis 30 days prior to admission among patients with affective disorder with psychotic features compared to patients with affective disorder without psychotic features?

3. Study Rationale:

The existing literature on cannabis use and psychosis has predominantly focused on non-affective psychotic disorders, especially schizophrenia. Research on the relationship between cannabis use and affective psychotic disorders is generally lacking. While evidence suggests that cannabis use is associated with non-affective psychotic disorders, it is unclear whether cannabis use is associated with affective psychotic diseases such as, MDD with psychotic features and BD with psychotic features. Additionally, while cannabis use has been shown to be associated with MDD and BD in adverse ways (e.g. greater risk of manic symptoms and depressive symptoms among those with MDD and BD, respectively), further research is required to investigate whether there is an association present among individuals with psychotic features among those with AD Examining the relationship between cannabis use and ADPF, if existent, is can inform future studies to investigate whether there is a shared underlying mechanism through which cannabis impacts individuals' likelihood of experiencing psychosis regardless of having an affective or non-affective mental disorder diagnosis. Otherwise, this could bring to question why cannabis use is not associated with the psychotic features present among those with a diagnosis of MDD or BD. Studying differences by age and gender are also under-researched.

To address the gaps in prior research, the study aimed to explore whether affective psychotic disorders are associated with cannabis use in an inpatient psychiatric population compared to individuals without ADPF. Population-level studies are lacking; including all acute inpatient psychiatric admission in Ontario will provide a population-level perspective of persons in psychiatric beds with ADPF compared to those without ADPF. As well, there are few studies on ADPF, with existing studies limited by varied measures of cannabis use (e.g. ever-use or lifetime use).(62,94) Measures based on lifetime or ever-use may be prone to recall bias and are unlikely to differentiate those who are frequent users. This limits the strength of associations and conclusions drawn from the studies. A past 30-day cannabis use indicator could mitigate these challenges. Finally, prior research on non-affective psychotic disorders has identified variations in the impact of other risk factors, such as age and gender, on the onset of psychosis.(39–42) It is unclear whether cannabis use and affective psychotic disorders vary based on such risk factors, as well. To study these nuances, it is important to explore whether age and/or gender are potential moderators in the association between cannabis use 30 days prior to admission. Addressing these knowledge gaps will inform future research on substance use and other risk factors related to cannabis use, policy directions and clinical practice among individuals with AD experiencing psychosis.

4. Methods:

4.1 Study Design and Data Source:

Data from the Ontario Mental Health Reporting System (OMHRS) were used to conduct a cross-sectional analysis of index admissions to inpatient psychiatry in Ontario between 2016 and 2019. The OMHRS is a database maintained by the Canadian Institute for Health Information (CIHI) and is based on RAI-Mental Health (RAI-MH) assessments completed on every person admitted to designated inpatient psychiatry beds in Ontario, Canada. During the first several days of a patient's stay, the clinicians overseeing the care of the patient collect information on their mental health condition through observation, by conducting interviews and by consulting key informants. Key informants include, family members, friends or others providing formal care to the patient in the process of administering the RAI-MH assessment.(95) Mental health professionals are trained and supported on an ongoing basis by clinical educators and CIHI to ensure reliable administration of the assessment tool.

4.1.1 Instrument:

The RAI-MH includes 396 items assessing patient demographics, mental and physical health status, functioning, patterns of substance use, and service utilization.(96) It has been mandated for use since 2005 among all persons admitted to inpatient psychiatry in Ontario. The assessment is completed at admission and discharge, as well as every 90-days for longer stay patients, by mental healthcare professionals overseeing the care of the person. The RAI-MH's validity and reliability have been studied extensively. Studies have demonstrated adequate inter-rater reliability across various care settings, in addition to the evaluation of face, content, convergent, criterion and predictive validity throughout the process of development and implementation of the assessment tool.(95–101) Hospitals submit the RAI-MH data to CIHI on a quarterly basis. To ensure data quality, CIHI conducts validity and data quality checks upon receipt of data submitted by facilities. For example, records with data quality issues are rejected and are expected to be resubmitted by facilities after implementing corrections.(102) Annually, through a data-sharing agreement, CIHI shares all OMHRS data with interRAI Canada at the University of Waterloo.

4.2 Study Sample:

The study included all admissions to acute inpatient psychiatry beds in Ontario between 2016 to 2019 with a DSM-5 BD or MDD diagnosis. The diagnoses were based on the discharge assessment, as coded by the diagnosis provided by the psychiatrist overseeing the care of the person (see Table 1 for

specific diagnoses included in this study). The data were restricted to include the most recent admission and discharge assessment for each person. The sample was restricted to include individuals admitted between 2016 and 2019 to control for changes between diagnostic criteria of BD and MDD between the DSM IV and DSM-5.

The study excluded individuals who were not considered to be acute patients (including patients in forensic beds or patients designated as forensic in the clinical record), patients under the age of 18, and patients with stays of less than 72 hours ("short stays"). Acute patients were included in the study sample as the majority of psychiatric admissions in Ontario are acute and to focus on admissions that are unplanned, at a vulnerable time in the person's care, particularly for those who have been admitted to inpatient psychiatry for the first time. Those in forensic psychiatry are admitted to inpatient psychiatry under court mandate, which influences their exposure to past 30-day cannabis use. The RAI-MH is mandated for use in adult psychiatric beds. Therefore, patients in these beds that are under the age of 18 are not representative of the target population of this service setting or assessment. Those admitted for less than 2 days were excluded as full RAI-MH assessments are not administered to short-stay patients, and a reliable diagnosis may not be available.

The total sample included 20,270 individuals with DSM-5 diagnoses of affective disorders admitted between Jan 1st, 2016, and Dec 31st, 2019. Ethics clearance for the thesis was provided by the University of Waterloo's Office of Research Ethics on May 28th, 2021, with the ORE file number 43280.

Table 1: DSM-5 List of Affective disorders including specifier for psychotic features (Bipolar and Related Disorder & Major Depressive Disorders)

DSM-5 CODE	DSM-5 Description
F06.33	Bipolar and Related Disorder Due to Another with manic features with manic or hypomanic-like episode
F06.34	Medical condition (manic or mixed)
F31.0	Bipolar I disorder, Current or most recent episode hypomanic
F31.11	Bipolar I disorder, Current or most recent episode manic, Mild
F31.12	Bipolar I disorder, Current or most recent episode manic, Moderate
F31.13	Bipolar I disorder, Current or most recent episode manic, Severe
F31.31	Bipolar I disorder, Current or most recent episode depressed, Mild
F31.32	Bipolar I disorder, Current or most recent episode depressed, Moderate
F31.4	Bipolar I disorder, Current or most recent episode depressed, Severe
F31.71	Bipolar I disorder, Current or most recent episode hypomanic, In partial remission
F31.72	Bipolar I disorder, Current or most recent episode hypomanic, In full remission
F31.73	Bipolar I disorder, Current or most recent episode manic, In partial remission
F31.74	Bipolar I disorder, Current or most recent episode manic, In full remission
F31.75	Bipolar I disorder, Current or most recent episode depressed, In partial remission
F31.76	Bipolar I disorder, Current or most recent episode depressed, In full remission
F31.2	Bipolar I disorder, Current or most recent episode manic, With psychotic features + Severe specifier
F31.5	Bipolar I disorder, Current or most recent episode depressed, With psychotic features + Severe specifier
F31.81	Bipolar II disorder
F31.89	Other specified bipolar and related disorder
F31.89	Other specified bipolar and related disorder + With mixed features specifier
F31.9	Unspecified bipolar and related disorder
F34.0	Cyclothymic disorder
F19.94	Substance/Medication-Induced Bipolar and Related Disorder
F32.0	Major depressive disorder, Single episode, Mild
F32.1	Major depressive disorder, Single episode, Moderate

F32.2	Major depressive disorder, Single episode, Severe
F32.4	Major depressive disorder, Single episode, In partial remission
F32.5	Major depressive disorder, Single episode, In full remission
F32.8	Other specified depressive disorder
F32.9	Unspecified depressive disorder
F33.0	Major depressive disorder, Recurrent episode, Mild
F33.1	Major depressive disorder, Recurrent episode, Moderate
F33.2	Major depressive disorder, Recurrent episode, Severe
F32.3	Major depressive disorder, Single episode, With psychotic features + Severe specifier
F33.3	Major depressive disorder, Recurrent Episode, With psychotic features + Severe specifier
F33.41	Major depressive disorder, Recurrent episode, In partial remission
F33.42	Major depressive disorder, Recurrent episode, In full remission
F33.9	Major depressive disorder, Recurrent episode, Unspecified
F34.1	Persistent depressive disorder (dysthymia)
F34.8	Disruptive Mood Dysregulation Disorder
F06.31	Depressive Disorder Due to another Medical Condition, With depressive features
F06.32	Depressive Disorder Due to another Medical Condition, With depressive-like episode
F06.34	Depressive Disorder Due to another Medical Condition, With mixed features
N94.3	Premenstrual Dysphoric Disorder

4.3 Variables:

The RAI-MH includes a range of variables based on individual items as well as embedded scales that combine items. Definitions of all variables are described below. In brief, the primary dependent variable was use of cannabis within 30-days of admission to inpatient psychiatry, including use within the 3 days and 7 days prior to admission. The primary independent variable of interest was affective disorder with psychotic features.

a) Affective disorder with psychotic features—Includes primary DSM-5 diagnoses of bipolar and related disorders and major depressive disorders (Table 1). To differentiate between affective disorder diagnoses with and without psychotic features, this variable was operationalized into a binary variable as "Yes" and "No". The "Yes" category was comprised of individuals with a diagnosis of affective disorder with psychotic features (bipolar disorder with psychotic features and major depressive disorder with psychotic features). All other bipolar and related disorders and major depressive disorders without psychotic features were included in the "No" group.

b) Past 30-day cannabis use—The substance use categories in the RAI-MH are scored based on the most recent use of the substance using the following categories: "never or more than 1 year ago", "within the last year", "within the last 3 months", "within the last month", "within the last 7 days", and "within the last 3 days". Substances include, inhalants, hallucinogens, cocaine and crack, stimulants, opiates, and cannabis. Cannabis was isolated to indicate whether a patient has used cannabis within the past month before admission to inpatient psychiatry. This variable was operationalized as a binary indicator as "Recent user" if the time of last substance use was reported as equal to or within the last month and as "No past month use" if the substance was never used or used within/more than a year ago. Information on substance use, including cannabis, was collected based on self-report, reports from others familiar with the person, and consultation with clinical record. In literature, cannabis use has been reported as use in the past 30-days as a cut off.(5,24) The RAI-MH does not capture the frequency of substance use. Past 30-day cannabis use can, however, be used as an indicator to indirectly measure the frequency of cannabis use, as individuals reporting past-month use are likely also to be frequent cannabis users.(5)

The following variables have been found to be correlated with cannabis use and were adjusted for as covariates: age group, gender, smoking status, alcohol use, misuse of over the counter or prescription medication in the prior 14 days, other substance use in the 30 days prior to assessment, other secondary and

tertiary DSM V diagnoses, cognitive performance, education level, marital status, year of admission to inpatient psychiatry and presence of mania or depressive symptoms.(5,58,60,81). To control for any intervention received in the community or during past hospitalizations among patients with AD, prior contact with community mental health services and prior psychiatric hospitalizations were included as covariates, as well. Additionally, bivariable analyses were conducted to identify differences between affective disorder with and without psychotic features. In addition to the list of covariates, variables related to demographic and clinical characteristics that were found to be significant were adjusted for, as well. Definitions for age, gender and other sample characteristics are outlined as follows:

c) Gender—The gender reported by the individual. A categorical variable including, "Male", "Female", and "Other". Dichotomized into a binary variable as "Male" and "Female". Those identifying as "other" were removed as the cell counts were too low to report.

d) Age Group—The OMHRS data contained the year of birth. The person's age was calculated by subtracting the year of birth from the year of assessment. Categorized into a variable with 7 categories including, "18-24", "25-34", "35-44", "45-54", "55-64", "65 and older". Both bipolar and related disorders and major depressive disorders can be chronic in nature and may reoccur after the first episode, including those with psychotic features.(77–80) Therefore, the age variable was grouped into categories to assess how it interacts with the affective disorder groups at various age ranges.

e) Education Level—Indicates the highest level of educational attainment of an individual. A categorical variable including, "No schooling", "8 grades or less", "9-11 grades", "High school", "Technical or trade school", "Some college/university", "Diploma/bachelor's degree", "Graduate degree", "Unknown". Categorized into a variable with 3 categories including, "less than high school", "completed high school" and "greater than high school".

f) Marital Status—Describes whether an individual is married, never married, has a partner or significant other, is widowed, separated, or divorced. Categorized into a variable with 3 categories, including, "never married", "married/partner/significant other" and "widowed/separated/divorced".

g) Employment status—A categorical variable indicating a patient's employment status. This includes the following 5 categories: "Employed", "Unemployed", "Seeking employment", "Unemployed, NOT seeking employment", "Other", and "Unknown". Operationalized into a binary variable as "Employed" if a patient was employed and "Not Employed" if the patient

indicated that they were “Unemployed”, “Seeking Employment”, “Unemployed, NOT seeking employment”, “Other” or “Unknown”.

h) Residential stability—A binary variable (“Yes” or “No”) indicating whether the most recent residence was temporary in nature.

i) Homelessness—A binary variable indicating a patient’s living arrangement at admission or post-discharge. If a patient was identified as homeless at admission or at discharge or homeless with or without living arrangements at a shelter post-discharge, they were categorized into the “Yes” category and “No” otherwise.

j) Past 30-day use of other substance(s)—Substances include, inhalants, hallucinogens, cocaine and crack, stimulants, and opiates; cannabis use was separated from this category. The substance use categories included: never or more than 1 year ago, within the last year, within the last 3 months, within the last month, within the last 7 days, and within the last 3 days. Dichotomized into a binary variable as “Recently used” for those who used any substances within the last month and “Did not use recently” otherwise.

k) Smoking—An ordinal variable indicating whether a person smokes or chews tobacco daily. It includes 3 categories including, “No”, “Yes”, and “Not in the last 3 days but is a daily smoker”. It was operationalized into a binary variable as, “Not a daily smoker” and “Daily Smoker/Did not smoke in past 3 days”.

l) Alcohol Use—An ordinal variable indicating the number of drinks an individual has consumed in any single sitting in the past 14 days prior to hospitalization. It includes 4 categories ranging from, none, 1, 2 to 4, and 5 or more. It was operationalized into a binary variable as “5 or more drinks” and “Less than 5 drinks”.

m) Misuse of Medication—A binary variable (“Yes” or “No”) whether a patient has misused prescription or over-the-counter medication in the 3 months prior to admission to inpatient psychiatry.

n) Cognitive performance—Based on the Cognitive Performance Scale (CPS), which assesses one’s cognitive status. An ordinal variable indicating the performance of one’s ability to make daily decisions, short-term memory, and ability to express oneself. Scores on the CPS range from 0 to 6, where higher scores indicate greater severity of cognitive impairment. This variable was dichotomized into a binary variable where scores >2 were considered to indicate the presence of cognitive impairment and scores ≤2 indicated absence of cognitive impairment.(71)

o) Past year community mental health service use—Indicates when a patient last had contact with a community mental health agency or mental health professional within the past year. It includes 3 categories: “No contact in the last year”, “31 days or more”, and “30 days or less”. This variable was operationalized into a binary variable indicating “Contact with mental health services” for those who had community mental health contact in the last 31 days or more or in the past 30 days or less or “No contact” for those who did not have contact in the last year”.

p) Number of lifetime admissions—Indicates the number of prior psychiatric admissions excluding current admission. It includes 3 categories: “None”, “1 to 3”, “4 to 5”, and “6 or more”. This variable was operationalized into a binary variable as “Yes” if a patient reports a history of psychiatric hospitalizations and “No” if none.

q) Year—A categorical variable which ranges from 2016 to 2019. This variable remained categorical.

r) Inpatient status—Indicates status at the time of admission. Includes 5 categories: “Application for psychiatric assessment (Exclude forensics)”, “Voluntary”, “Involuntary”, “Informal”, and “Forensic”. This variable was operationalized into 3 separate binary variables for “Involuntary”, “Voluntary” and “Informal” status’. “Application for psychiatric assessment (Exclude forensics)”, and “Involuntary” were combined into “Involuntary” status, and patients with forensic status were excluded from the sample.

s) Other Secondary or Tertiary Diagnoses—Indicates secondary or tertiary diagnoses of DSM-5 psychiatric disorders. Operationalized as a binary variable as “Yes” if a patient had a diagnosis of at least one secondary or tertiary diagnosis and “No” otherwise.

t) Symptoms of mania—Based on the Mania Scale assessing one’s experience of inflated self-worth, hyperarousal, increased ability to socialize/hypersexuality, pressured speech patterns, labile affect and presence of sleep problems related to hypomania. Scores range from 0 to 20, where higher scores indicated greater severity of manic symptoms. This variable remained continuous.

u) Symptoms of depression—Based on the Depression Severity Index (DSI), which assesses an individual’s expression of depression, including the following: facial expression of sadness or pain, expression of negative feelings, self-deprecating statements, statements of guilt/shame, and feelings of hopelessness. Scores on the DSI range from 0 to 3 based on the frequency of

exhibiting depressive expressions in the last 3 days. The higher categories indicate greater severity of depressive symptoms. The variable remained continuous.

v) Positive Symptoms—Based on the Positive Symptom Scale (PSS) indicating presence of positive symptoms of psychosis. Scores range from 0-12, where higher scores indicate greater severity of symptoms. This variable remained continuous.

4.4 Statistical Analyses:

Statistical Analysis Software (SAS) version 9.3 was used to perform all analyses. PROC FREQ and PROC MEANS procedures were used to assess sample characteristics of patients included in the study sample using means, standard deviations and 95% CIs for continuous variables, and frequencies for categorical variables. Bivariable analyses were conducted between sample characteristics and affective disorders with/without psychotic features using Chi-square tests for categorical variables, and mean, 95% confidence intervals, and standard deviations for continuous variables of interest.

Covariates included, age, gender, education level, marital status, employment status, other substance use, medication misuse, smoking status, problematic alcohol use, prior contact with community mental health services, prior hospitalizations, homelessness, temporary residence, cognitive performance, year, other diagnoses, depressive symptoms, manic symptoms, voluntary admission status, and involuntary admission status.

Logistic regression analyses were performed to assess whether affective disorder with psychotic features were associated with cannabis use 30 days prior to admission to inpatient psychiatry. Regression coefficients, odds ratios (OR), and 95% confidence intervals (CI) of cannabis use prior to admission while controlling for all covariates were calculated for each model using the PROC LOGISTIC procedure. The concordance statistic (C-statistic) was be used to evaluate the overall fit of each model.

<u>Research Question 1:</u>

Firstly, Model 1, or the base model, was developed to calculate the unadjusted odds of having used cannabis prior to admission. The variable for affective disorder was included in the regression model and no covariates were included. The unadjusted odds of having used cannabis 30 days prior to hospitalization among those with ADPF were calculated using the PROC LOGISTIC procedure compared to those without ADPF. Model 2, or the main effects model, was then developed to calculate the regression coefficients, p-values, OR estimates, and 95% CIs. Covariates were all included in the model in one block, including age and gender.

Research Question 1a:

For research question 1a, the interaction term between age and affective disorder was added to the main effects model (Model 2) to assess whether age moderated the association between ADPF and past 30-day cannabis use to develop Model 3. All covariates from Model 2, including age, remained in this model. If the regression coefficients and p-values (<0.05) for the interaction term were found to be significant, age would be reported as a moderator between affective disorder and cannabis use 30 days prior to admission while controlling for covariates. The main effects model (Model 2) would not be interpreted due to the presence of the interaction.

Research Question 1b:

For research question 1b, the interaction term between gender and affective disorder was included in the main effects model (Model 2) to assess whether gender moderated the association between cannabis use 30 days prior to admission and ADPF compared to those without ADPF. If the correlation coefficient and p-value (<0.05) of the interaction term was found to be significant, gender would be reported as a moderator between ADPF and cannabis use 30 days prior to admission while controlling for covariates. The main effects model (Model 2) would not be interpreted due to the presence of the interaction.

5. Results

5.1 Sample Characteristics:

Sample characteristics are listed in Table 2. Between January 1, 2016, to December 31, 2019, there were 20,270 individuals admitted to inpatient psychiatry in Ontario with a diagnosis of an AD, out of which 2,876 individuals had an ADPF and 17,394 individuals were diagnosed without ADPF. 1,485 individuals had a DSM-5 diagnosis of BD with psychotic features and 5,906 had a diagnosis of BD without psychotic features. 1,391 individuals had a DSM-5 diagnosis of MDD with psychotic features and 11,488 individuals had a diagnosis of MDD without psychotic features. The approximate mean age of the sample was 45 years (SD=17.5) and 42.9% were male. The sample size of those identifying as non-binary was too low to report (<5) and was therefore excluded from the sample. Just over half (59.2%) had an education level higher than the high school level, and 45.0% were never married, while 19.1% were either widowed, separated or divorced. Among those with AD, 21.8% of individuals' most recent residence was reported as temporary, and 4.0% out of the whole sample experienced homelessness at the time of admission. 31.4% of individuals were employed, while 68.6% reported being unemployed and seeking employment, unemployed and not seeking employment, other or their employment status was unknown.

Cannabis was the most frequently reported substance used within 30 days of admission at 23.0%, followed by 4.5% of individuals who reported cocaine and crack use, 2.8% reported opiate use, 2.4% reported stimulant use, 0.7% reported hallucinogen use, and 0.4% reported inhalant use. Additionally, 30.3% were daily smokers, 10.4% reported consumption of >5 alcoholic drinks in a single sitting within 14 days prior to admission, and 12.8% reported medication misuse in the 3 months prior to admission to inpatient psychiatry.

The sample experienced moderate to severe depression, with a mean DSI scale of 4.72 (SD=4.0). The average mania scale score of 2.80 (SD=4.1) indicated moderate symptoms, while the mean PSS Short score of 1.60 indicated that 1 to 2 positive symptoms had been experienced in the 3 days prior to assessment (SD=2.5). Regarding patients' lifetime history of psychiatric hospitalizations, 59.9% had at least one prior admission to inpatient psychiatry, out of which 40.7% had 1-3 admissions, 10.6% had 4-5, and 8.6% had had 6 or more. Moreover, about half of patients had no contact with community mental health services in the past year (49.8%), while 17.3% had made contact within the last 30 days and 32.8% had contact >31 days ago. At admission, 68.5% of patients were involuntarily admitted, while 31.1% were voluntarily admitted to inpatient psychiatry.

Table 2: Sample Characteristics (n = 20,270)

Variable	Response	N or Mean	% Or SD
Affective Disorder with Psychotic Features	Yes	2876	14.2
	No	17394	85.8
Major Depressive Disorder/Bipolar Disorder Diagnosis	MDD with Psychotic Features	1391	6.86
	MDD without Psychotic Features	11488	56.67
	BD with Psychotic Features	1485	7.33
	BD without Psychotic Features	5906	29.14
Gender	Male	8693	42.9
	Female	11577	57.1
Age	18-24	3089	15.2
	25-34	3440	17.0
	35-44	3177	15.7
	45-54	3790	18.7
	55-64	3770	18.6
	65+	3004	14.8
Education Level	Less than high school or Unknown	2633	13.0
	Married or partner/ significant other	5638	27.8
	Widowed, separated or divorced	11999	59.2
Marital Status	Never Married	9129	45.0
	Married or partner or significant other	7276	35.9
	Widowed, separated, divorced	3865	19.1
Employment Status	Not Employed	13897	68.6
	Employed	6373	31.4
Residential Stability	Most recent was not temporary	15847	78.2

	Most recent was temporary	4422	21.8
Homelessness	Yes	808	4.0
	No	19462	96.0
Past Year Community Mental Health Service Use	No Contact (past year)	10099	49.8
	Contact 31+ days	3515	17.3
	Contact less than 30 days	6656	32.8
Prior Admissions	Yes	12138	59.9
	No	17679	40.12
Number of Lifetime Admissions	None	8132	40.1
	1 to 3	8255	40.7
	4 to 5	2138	10.6
	6 or more	1745	8.6
Year	2016	4261	21.1
	2017	4781	23.6
	2018	5221	25.8
	2019	6007	29.6
Cognitive Performance	No presence of cognitive Impairment	19518	96.3
	Presence of cognitive impairment	752	3.7
Symptoms of Mania		Mean=2.81 (95% CI=2.75-2.86)	SD=4.2
Symptoms of Depression		Mean=4.73 (95% CI=4.67-4.78)	SD=4.0
Positive Psychotic Symptoms		Mean=1.60 (95% CI=4.67-4.78)	SD=2.5
Other Secondary or Tertiary Diagnosis	Yes	5964	29.4

	No	14306	70.6
Past 30-Day Substance Use			
Cannabis	Yes	4652	22.9
	No	15618	77.1
Inhalant	Yes	85	0.4
	No	20185	99.6
Hallucinogens	Yes	146	0.7
	No	20124	99.3
Cocaine Crack	Yes	906	4.5
	No	19364	95.5
Stimulants	Yes	495	2.4
	No	19775	97.6
Opiates	Yes	566	2.8
	No	19704	97.2
Medication Misuse	Yes	2591	12.8
	No	17679	87.2
Smoking	Yes	6134	30.3
	No	14136	69.7
Problematic Alcohol Use	Yes	2115	10.4
	No	18155	89.6
Inpatient Status at Time of Admission			
Involuntary	Yes	13890	68.52
	No	6380	31.5
Voluntary	Yes	6302	31.1
	No	13968	68.9
Informal	Yes	78	0.4
	No	20192	99.6

5.2 Descriptive Statistics of Individuals with Affective Disorders with and without Psychotic Features:

Bivariable analyses describing the sample characteristics between affective disorders with and without psychotic features up are listed in Table 3. There was no statistically significant difference in cannabis use 30 days prior to admission to inpatient psychiatry between the affective disorder groups (Chi-square=0.0000, p-value=0.9982). 23.0% without and 23.0% with psychotic features reported cannabis use 30 days prior to admission among individuals with affective disorder. The mean age of those with ADPF was 46 years (SD=17.25, 95% CI=45.78-47.04). Among those without ADPF, 42.7% of individuals admitted to inpatient psychiatry were male, and 57.3% were female. Similarly, among those with ADPF, 43.9% were male and 56.1% were female (Chi-Square=1.35, p-value=0.2448).

Several factors were significantly associated with affective disorders with and without psychotic features, indicating that the two groups differed in a number of characteristics. These included: age, marital status, employment, status, recent cocaine and crack use, recent opiate use, problematic alcohol use, smoking, medication misuse, history of lifetime admissions to inpatient psychiatry, tertiary and secondary psychiatric DSM-5 diagnoses, year, contact with community mental health services, homelessness, residential stability, cognitive decline, involuntary admission status, voluntary admission status, symptoms of mania, symptoms of depression and positive psychotic symptoms.

The association between the affective disorder groups and the following variables were not statistically significant: education level, informal admission status, recent inhalant use, recent hallucinogen use, and recent stimulant use.

Table 3: Bivariable Analyses of Sample Characteristics between those with or without Affective Disorder with Psychotic Features

Variable	Response	Prevalence of ADPF (No)	Prevalence of ADPF (Yes)	Chi-Square or SD	P-Value
		N (%)	N (%)		
Gender	Male	7431 (42.7)	1262 (43.9)	1.35	0.2448
	Female	9963 (57.3)	1614 (56.1)		
Age	18-24	2757 (15.9)	322 (11.5)	48.71	<.0001
	25-34	2888 (16.6)	552 (19.2)		
	35-44	2707 (15.6)	470(16.3)		
	45-54	3252 (18.7)	538 (18.7)		
	55-64	3261 (18.8)	509 (17.7)		
	65+	2529 (14.5)	475 (16.5)		
Education Level	Less than high school or Unknown	2233 (12.8)	400 (13.9)	3.59	0.1665
	Completed high school	4869 (28.0)	769 (26.7)		
	Greater than high school	10292 (59.2)	1707 (59.4)		
Marital Status	Never Married	7888 (45.4)	1241 (43.2)	17.01	0.0002
	Married or partner or significant other	6147 (35.3)	1129 (39.3)		
	Widowed, separated, divorced	3359 (19.3)	506 (17.6)		
Employment Status	Not Employed	11783 (67.7)	2114 (73.5)	38.03	<.0001
	Employed	5611 (32.3)	762 (26.5)		
Residential Stability	Most recent was not temporary	13525 (77.8)	2322 (80.7)	12.85	0.0003
	Most recent was temporary	3869 (22.2)	554 (19.3)		
Homelessness	Yes	719 (4.1)	89 (3.1)	6.96	0.0083
	No	16675 (95.9)	2787 (96.9)		

Past Year Community Mental Health Service Use	No Contact (past year)	8583 (49.3)	1516 (52.7)	13.25	0.0013
	Contact 31+ days	3021 (17.4)	494 (17.1)		
	Contact less than 30 days	5790 (33.3)	866 (30.1)		
Prior Admissions	Yes	10274 (59.1)	1864 (64.8)	33.92	<.0001
	No	7120 (40.9)	1012 (35.2)		
Number Of Lifetime Admissions	None	7120 (40.9)	1012 (35.2)	37.92	<.0001
	1 to 3	6967 (40.1)	1288 (44.8)		
	4 to 5	1803 (10.4)	335 (11.7)		
	6 or more	1504 (8.7)	241 (8.4)		
Year	2016	3646 (21.0)	615 (21.4)	8.39	0.0385
	2017	4156 (23.9)	625 (21.7)		
	2018	4486 (25.8)	735 (25.6)		
	2019	5106 (29.4)	901 (31.3)		
Cognitive Performance	No presence of cognitive Impairment	16927 (97.3)	2591 (90.1)	360.61	<.0001
	Presence of cognitive impairment	467 (2.7)	285 (9.9)		
Other Secondary or Tertiary Diagnosis	Yes	5293 (30.4)	671 (23.3)	59.89	<.0001
	No	12101 (69.6)	2205 (76.7)		
Past 30-Day Substance Use					
Cannabis	Yes	3992 (23.0)	660 (23.0)	0.00	0.9982
	No	13402 (77.0)	2216 (77.0)		
Inhalant	Yes	71 (0.4)	14 (0.5)	0.37	0.5457
	No	17323 (99.6)	2862 (99.5)		
Hallucinogens	Yes	124 (0.7)	22 (0.8)	0.09	0.7597

	No	17270 (99.3)	2854 (99.2)		
Cocaine Crack	Yes	830 (4.8)	76 (2.6)	26.2	<.0001
	No	16564 (95.2)	2800 (97.4)		
Stimulants	Yes	424 (2.4)	71 (2.5)	0.01	0.9203
	No	16970 (97.6)	2805 (97.5)		
Opiates	Yes	521 (3.0)	45 (1.6)	18.61	<.0001
	No	16873 (97.00)	2831 (98.44)		
Medication Misuse	Yes	2396 (13.8)	195 (6.8)	108.30	<.0001
	No	14998 (86.2)	2681 (93.2)		
Smoking	Yes	5380 (30.9)	754 (26.2)	25.98	<.0001
	No	12014 (69.1)	2122 (73.8)		
Alcohol Use – 5 Or More Drinks	Yes	1937 (11.1)	178 (6.2)	64.62	<.0001
	No	15457 (88.9)	2698 (93.8)		
Inpatient Status at Time of Admission					
Involuntary	Yes	11580 (66.6)	2310 (80.3)	216.18	<.0001
	No	5814 (33.4)	566 (19.7)		
Voluntary	Yes	5744 (33.0)	558 (19.4)	213.72	<.0001
	No	11650 (67.0)	2318 (80.6)		
Informal	Yes	70 (0.4)	8 (0.3)	0.99	0.3187
	No	17324 (99.6)	2868 (99.7)		

	Prevalence of ADPF (No)		**Prevalence of ADPF (Yes)**	
	Mean (SD)	**95% CI**	**Mean (SD)**	**95% CI**
Symptoms of Mania	2.57 (3.9)	2.51-2.63	4.23 (4.9)	4.05-4.41
Symptoms of Depression	4.87 (4.1)	4.81-4.93	3.84 (3.8)	3.70-3.98

Positive Psychotic Symptoms	1.25 (2.2)	1.22-1.29	3.69 (3.1)	3.58-3.80

5.3 Binary Logistic Regression Analyses Results

5.3.1 Research Question 1:

Among adults with affective disorders admitted to inpatient psychiatry in Ontario between 2016 and 2019, are those with affective disorder with psychotic features at greater odds of having used cannabis 30 days prior to admission compared to patients with affective disorder without psychotic features?

Table 4 presents the ORs, 95% CIs and C-statistics of two logistic regression models examining the association between ADPF and cannabis use in the 30 days prior to admission. In the bivariable model (Model 1) the OR was 1 (95% Wald CI=0.910-1.098), the base model containing only the AD diagnosis variable in relation to cannabis use. The regression coefficient for AD diagnosis was 0 (SE=0.0479, p-value=1.000). At bivariable level, AD diagnosis was not associated with cannabis use 30 days prior to admission.

Next, the main effects model, **Model 2,** included all covariates to the base model (Model 1 + covariates). The regression coefficient for the AD diagnostic group was -0.0191 (SE=0.0577, p-value=0.7411). Holding all covariates constant, having ADPF was not associated with greater odds of cannabis use 30-days prior to admission (OR=0.981, 95% Wald CI=0.877-1.099) compared to those without ADPF. The C-statistic for Model 2 was found to be 81.3.

5.3.2 Research Question 1a:

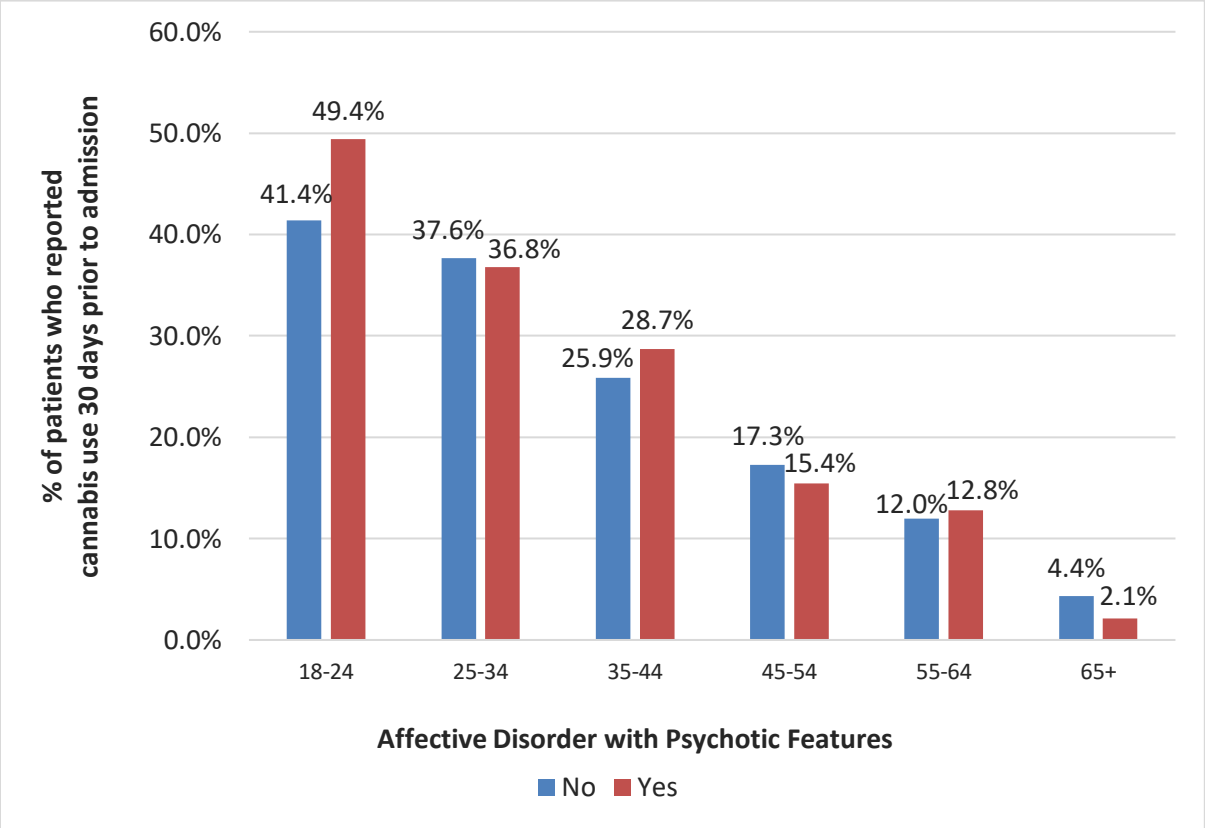
Does age modify the odds of having used cannabis 30 days prior to admission among patients with affective disorder with psychotic features compared to patients with affective disorders without psychotic features?

Model 3 tested the interaction between age and AD diagnosis while controlling for covariates. The regression coefficients of the interaction between affective disorder and age (vs 18-24-year-olds) were -0.2137 (SE=0.1665, p-value=0.1994) for 25–34-year-olds, -0.0242 (SE=0.1775, p-value=0.8917) for 35-44-year-olds, -0.2063 (SE=0.1886, p-value=0.2740) for 45-54-year-olds, 0.0729 (SE=0.1990, p-value=0.7143) for 55-64-year-olds and -0.8798 (SE=0.3632, p-value=0.0154) for those over 65 years old. The C-statistic for Model 3 was found to be 81.3.

Therefore, age did not modify the odds of having used cannabis 30 days prior to admission among those with ADPF compared to those without ADPF while controlling for covariates. Figure 1 displays a

positively skewed distribution of cannabis use rates by age groups. The proportions of those with AD who used cannabis 30 days prior to admission were greatest among 18–24-year-olds. However, for all other age groups, of the proportion who used cannabis 30 days prior to admission was similar between those with AD with and without psychotic features.

Figure 1: Percentage of patients who reported cannabis use 30 days prior to admission to inpatient psychiatry among those with and without affective disorder with psychotic features by age group



5.3.3 Research Question 1b:

Does gender modify the odds of having used cannabis 30 days prior to admission among patients with affective disorder with psychotic features compared to patients with affective disorder without psychotic features?

Model 4 tested the interaction between gender and AD while controlling for covariates. The regression coefficient for the interaction term was -0.3409 (SE=0.1125, p-value=0.0025). The C-statistic for Model 4 was found to be 81.3.

Gender was found to modify the odds of having used cannabis 30 days prior to admission among those with ADPF compared to those without ADPF while controlling for covariates. In other words, the odds of having used cannabis prior to admission among those with ADPF did differ between males and females compared to those without ADPF. The odds of having used cannabis were higher among males with ADPF compared to females with ADPF.

Table 5 presents the ORs for the interaction between gender and AD diagnosis. The odds of cannabis use 30 days prior to admission were lower among females with AD without (OR=0.693) and with psychotic features (OR=0.579) compared to males without ADPF who were not cannabis users 30 days prior to admission. Males with ADPF were at higher odds (OR=1.155) of having used cannabis prior to admission compared to males without ADPF.

Table 4: Binary Logistic Regression Analyses for the association between cannabis use 30 days prior to admission and affective disorder diagnosis and interactions Models 1 and 2

	Model 1: OR (95% CI)	Model 2: OR (95% CI)
C-Statistic	-	81.3
Affective Disorder with Psychotic Features (Yes vs No)	1.000 (0.910-1.098)	0.981 (0.876-1.099)
Age (vs 18-24)		
25-34		0.712 (0.636-0.798)
35-44		0.424 (0.373-0.482)
45-54		0.253 (0.221-0.290)
55-64		0.183 (0.158-0.212)
65+		0.072 (0.058-0.090)
Gender (Female vs Male)		0.670 (0.621-0.724)
Education Level (vs High school or Unknown)		
Highschool		0.824 (0.728-0.934)
More than Highschool		0.819 (0.729-0.920)
Marital Status (vs Never married)		
Married or partner/significant other		0.882 (0.799-0.974)
Widowed, separated, divorced		0.948 (0.838-1.073)
Employment Status (Employed vs Not employed)		0.956 (0.880-1.038)
Involuntary		1.468

(Involuntary vs Not involuntary)	(0.785-2.745)
Voluntary (Voluntary vs Not voluntary)	1.417 (0.755-2.659)
Residential Stability (Most recent residence temporary vs Not temporary)	0.993 (0.905-1.089)
Homelessness	1.051 (0.879-1.256)
Additional Past 30-Day Substance Use (Any vs No additional past 30-day substance use)	2.919 (2.587-3.295)
Medication Misuse (Misuse in the last 3 months vs No-misuse in the last 3 months)	1.025 (0.916-1.148)
Smoking Status (Daily smoker or daily smoker but not in the past 3 days vs Not a daily smoker)	3.196 (2.950-3.463)
Problematic Alcohol Use (5+ drinks vs Less than 5+ drinks in one sitting in past 14 days)	1.404 (1.255-1.570)
Past Year Community Mental Health Service Use (vs No past year contact)	
Contact 31+ days	0.932 (0.837-1.038)
Contact less than 30 days	0.866 (0.791-0.948)
Prior Admissions (Prior admissions vs No prior admissions)	0.929 (0.855-1.010)

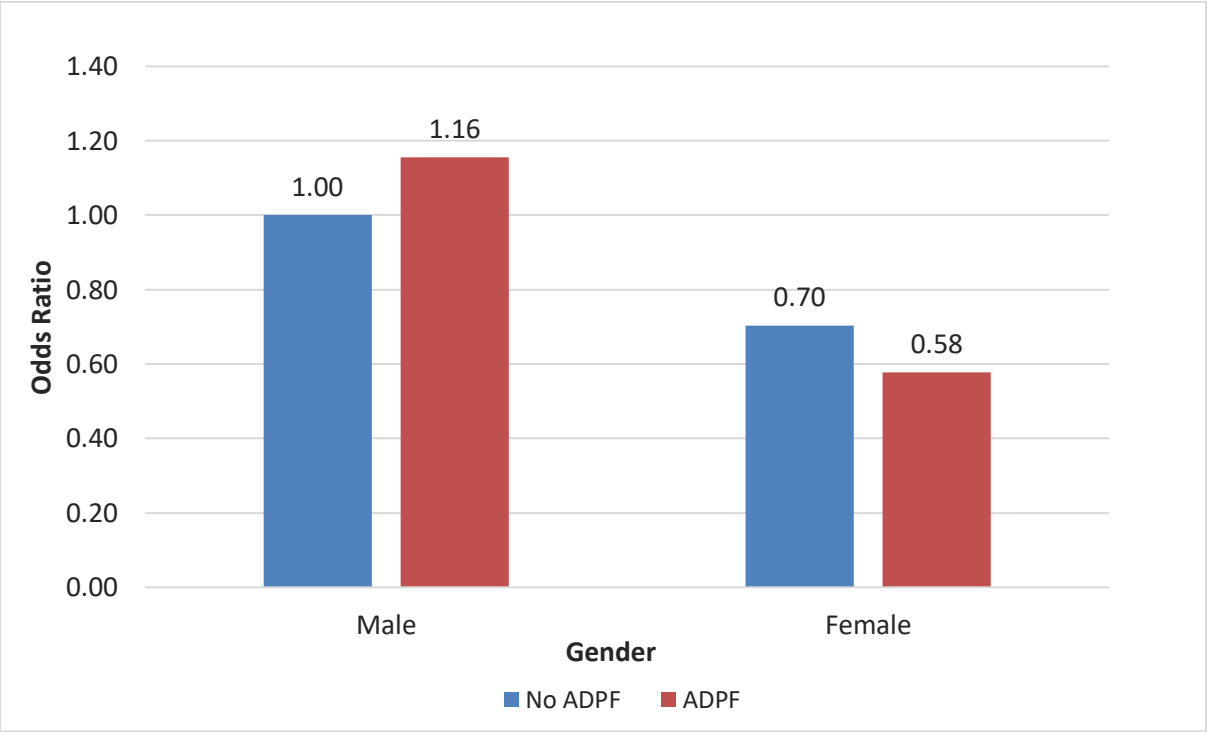
Cognitive Performance (Presence vs Absence of cognitive impairment)	0.895 (0.709-1.129)
Year (vs 2016)	
2017	1.279 (1.137-1.437)
2018	1.369 (1.221-1.534)
2019	1.536 (1.376-1.716)
Other Secondary or Tertiary Diagnosis (Diagnosis vs No secondary or tertiary diagnosis)	1.378 (1.271-1.493)
Symptoms of Depression	0.992 (0.982-1.001)
Symptoms of Mania	1.089 (1.080-1.099)

Covariates for Model 2: age, gender, education level, marital status, employment status, other substance use, medication misuse, smoking status, problematic alcohol use, prior contact with community mental health services, prior hospitalizations, homelessness, temporary residence, cognitive performance, year, other diagnoses, depressive symptoms, manic symptoms, voluntary admission status, and involuntary admission status.

Table 5: Odds Ratios for each level of interaction between gender and affective disorder with psychotic features

		Affective Disorder with Psychotic Features	
		No (OR)	**Yes (OR)**
Gender	Male	1.00	1.155
	Female	0.693	0.579

Figure 2: Odds ratios for the interaction between affective disorder with psychotic features and gender at each level of interaction



5.3.4 Gender-Stratified Models:

To further interpret the effect modification of gender in the association between ADPF and cannabis use, stratified adjusted models were developed for each gender. Table 6 presents the ORs, 95% CIs and C-statistics of the gender-stratified logistic regression models. **Model 5** was the main effects model for males, and **Model 6** was the main effects model for females (Table 6). For Model 5, the regression coefficient for the AD diagnostic group was 0.1406 (SE=0.0788, p-value=0.0743). Holding all covariates constant, being male with a diagnosis of an ADPF was not associated with the odds of cannabis use 30 days prior to admission (OR=1.151, 95% Wald CI=0.986-1.343). The C-statistic for Model 5 was found to be 79.7.

Lastly, the regression coefficient for the AD diagnostic group was -0.1851 (SE=0.0863, p-value=0.0320) for Model 6. Holding all covariates constant, being female with a diagnosis of an ADPF was associated with a decrease in the odds of having used cannabis 30 days prior to admission compared to females without ADPF (OR=0.831, 95% Wald CI=0.702-0.984). The C-statistic for Model 6 was found to be 81.8.

Therefore, females with an AD diagnosis with psychotic features were at 0.831 times lower odds or 16.9% less likely to have used cannabis 30 days prior to admission compared to females without ADPF while controlling for covariates.

Table 6: Gender-stratified binary logistic regression analysis of the association between ADPF and cannabis uses 30 days prior to admission to inpatient psychiatry

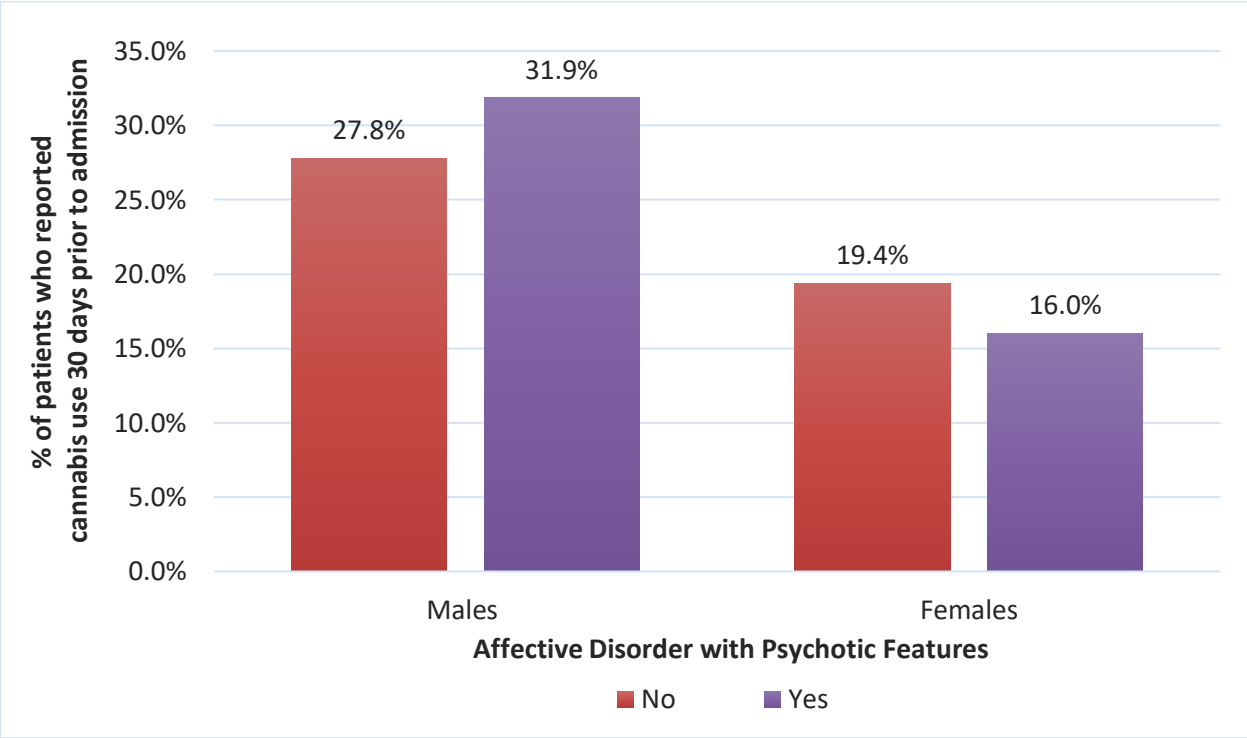
Model	OR	95% CI	C-Statistic
Model 5: Affective Disorder with Psychotic Features - Males	1.151	0.986-1.343	79.7
Model 6: Affective Disorder with Psychotic Features - Females	0.831	0.702-0.984	81.8

*__Covariates__: age, education level, marital status, employment status, other substance use, medication misuse, smoking status, problematic alcohol use, prior contact with community mental health services, prior hospitalizations, homelessness, temporary residence, cognitive performance, year, other diagnoses, depressive symptoms, manic symptoms, voluntary admission status, and involuntary admission status.

Figure 3 shows the proportions of those with AD who used cannabis within 30 days of admission, by gender. There was a greater proportion of patients who reported cannabis use 30 days prior to admission among males with ADPF (31.9%) compared to males without ADPF (27.8%). The opposite trend was

observed for females, where a lower proportion of female patients with ADPF reported cannabis use 30 days prior to admission (16.0%) compared to females without ADPF (19.4%).

Figure 3: Percentage of patients who reported cannabis use 30 days prior to admission to inpatient psychiatry among those with affective disorder with and without psychotic features by gender



5.3.5 Sensitivity Analysis:

A sensitivity analysis was performed by analyzing the models using a narrower definition of cannabis use. Instead of using a past 30-day cannabis use indicator, the variable was modified to a past 7-day use indicator for cannabis, considering that a past 30-day use indicator includes those who may have sparsely used cannabis a month prior to hospitalization. Overall, 3672 (18.1%) individuals reported cannabis use within 7 days prior to admission to inpatient psychiatry. At a bivariable level, there was no difference in rates of cannabis use between the affective disorder with and without psychotic feature groups. Among those with ADPF, 18.5% reported cannabis use within 7 days prior to admission. Similarly, 18.1% of those without ADPF reported cannabis use within 7 days prior to admission. Upon re-running the same regression models with the past 7-day use variable, the results remained unchanged compared to the original analyses conducted with the past 30-day cannabis use indicator. The ORs of the gender-stratified models were not statistically significant and significant for Models 5 and 6, respectively (see Table 7).

Table 7: Sensitivity analysis of gender-stratified binary logistic regression analysis of the association between cannabis uses 30 days prior to admission to inpatient psychiatry and affective disorder diagnosis

Model	OR	95% CI	C-statistic
Model 5: Affective Disorder with Psychotic Features - Males	1.159	0.986-1.362	79.8
Model 6: Affective Disorder with Psychotic Features - Females	0.833	0.695-0.999	80.8

*__Covariates__: age, education level, marital status, employment status, other substance use, medication misuse, smoking status, problematic alcohol use, prior contact with community mental health services, prior hospitalizations, homelessness, temporary residence, cognitive performance, year, other diagnoses, depressive symptoms, manic symptoms, voluntary admission status, and involuntary admission status.

6. Discussion

This research examined whether persons diagnosed with ADPF were more likely to have used cannabis prior to admission to inpatient psychiatry compared to persons without ADPF. Unlike literature on the impact of cannabis use on non-affective psychotic disorders, research on BD and MDD with psychotic features is sparse. In addressing this gap, this study identified a nuanced association between ADPF and cannabis use. Overall, individuals diagnosed with ADPF were at no greater odds of having used cannabis 30 days prior to admission to inpatient psychiatry compared to those without ADPF. However, gender significantly moderated the association between ADPF and cannabis. On the other hand, age was not found to moderate the association between cannabis use and AD diagnosis.

The finding that, as a main effect, there was no statistically significant association between ADPF, and cannabis use in the 30 days prior to admission was consistent with several studies on affective psychotic disorders while conflicting with others. For instance, Manrique-Garcia et al.'s(62) study among Swedish military servicemen assessed lifetime cannabis use among young adults aged 18 to 20 years using an ever-use use indicator. The indicator was coupled with follow-up questions regarding frequency among those with bipolar disorder or affective psychosis as a combined outcome. The study did not find a statistically significant association between cannabis use and bipolar disorder/affective psychosis diagnosis at follow-up. On the other hand, Mustonen et al.(94)found a statistically significant association between psychotic depression and using cannabis within their lifetime among adolescents. Cannabis use was measured as an ever-use indicator similar to Manrique-Garcia et al.'s study.(62) Other studies have also found an association between psychotic symptoms and experiences of psychotic episodes over a lifetime among individuals with bipolar disorders who reported cannabis use.(77,92,93) Although results and methodologies across prior literature vary, further research distinctly focusing on BD with psychotic features and MDD with psychotic features is needed. Variations in measuring cannabis use and aggregating psychotic BD or MDD with non-psychotic MDD and BD can limit comparability across studies.

There are a number of possible explanations for finding a lack of association for the main effects model (Model 2). Primarily, the presence of a gender-based interaction is a reason why there was no association between ADPF as a main effect and cannabis use. Another factor to consider is the presence of recall bias which may have led to the under or overestimation of the length of time prior to admission a patient consumed cannabis (e.g., they state they used cannabis 40 days prior to rather than 25 days prior to admission). This may indicate that the estimated consumption rates are conservative and do not capture all

individuals who used cannabis prior to admission. The stigma around disclosure of cannabis use or a reluctance to disclose cannabis use due to mental health symptoms (e.g., paranoia) could have restricted reporting of cannabis, particularly among persons diagnosed with psychotic features. However, the sensitivity analysis of more recent use produced consistent results, indicating that response bias may not have been related to a lack of variation in the proportion of patients with AD who reported use of cannabis prior to admission. The past 30-day cannabis use variable may be capturing most, if not all, of those who were frequent cannabis users. This may explain why the study results remained the same after re-running the regression models with a more stringent definition of cannabis exposure.

While the association between ADPF and cannabis use prior to admission was not significant, the association may be moderated by other factors. Indeed, this study found that gender modified the association between ADPF and the use of cannabis prior to admission. Males used cannabis more often than females, particularly males with ADPF. Interestingly, being female with ADPF was protective against cannabis use within 30 days prior to hospitalization compared to females without ADPF. The sample consisted of more females (57.1%) than males (42.9%), while more males than females reported cannabis use, which is consistent with literature.(5,16) These findings align with prior research on cannabis use among males and females admitted to inpatient psychiatry. For instance, McGuckin et al.(24) found a statistically significant interaction between schizophrenia and other psychotic disorders, and gender. A greater proportion of males with psychotic disorder reported cannabis use 30 days prior to hospitalization compared to males without a psychotic disorder, and a lower proportion of females with psychotic disorder reported cannabis use than females without a psychotic disorder. Together, the study's findings combined with those of McGuckin et al.(24) reflect differences in the patterns of cannabis use between genders and the potential impact of cannabis on those experiencing psychosis.

Differences in the patterns of cannabis use between males and females may explain why being a female with ADPF was protective of having used cannabis prior to hospitalization compared while the association was not significant among males. The direction of the association suggests that there is a possibility of there being a positive association between cannabis use and ADPF among males. However, findings must be interpreted while keeping in mind that the 95% confidence interval of the OR for the main effects model for males (Model 5) overlapped with the null value. The direction of the associations observed between the genders aligns with prior literature on patterns of substance use between males and females. Males have been found to be more likely to engage in frequent use and at an earlier age of initiation compared to females.(5,16) Many report cannabis use for recreational and medical reasons.(12,68,103–

105) Although the reasons for use among those who reported cannabis use prior to admission in this study are unknown, findings may be explained by gender-based differences in motives for cannabis use. While there is some evidence noting the differences in cannabis use between men and women involving gender roles that influence the initiation of use, gender-based research on motives for cannabis use needs further study beyond prevalence and trends in usage.(106,107) Rates of CUD have also been found to be more likely to occur among males with serious mental illnesses (e.g. schizophrenia, psychotic disorders, mood and substance use disorders) compared to females with serious mental illness.(67) Compared to females without serious mental illnesses, the likelihood of having CUD was greater among females with all comorbid serious mental illnesses except for schizophrenia, other psychotic disorders and depression. These patterns in rates of cannabis consumption and the associations found in Kozak et al.'s(67) study reiterate the ways in which cannabis use varies between males and females. As discussed in Kozak et al.'s(67) study, biological differences linked with the development of the endocannabinoid system and genetic factors (e.g. genetic polymorphisms that are associated with both psychotic disorders and cannabis use)(42,48) in addition to behavioural differences could be playing a role in shaping mental health outcomes by gender.

Genetic differences related to the ways in which cannabinoids are metabolized among males vs females may have accounted for gender-based moderation between cannabis exposure and ADPF. Studies among those with non-affective psychotic disorders suggest that the association between cannabis exposure and age of onset of psychosis are influenced by underlying genetic factors (e.g. genetic polymorphisms that are associated with psychotic disorders and cannabis use).(42,48) In Decoster et al.'s(42) study, cannabis use was associated with earlier age of onset regardless of genetic factors among males, whereas age of onset of psychosis was found to occur earlier among females due to the interaction effect between certain genetic polymorphisms (i.e. BDNF Val66Met) and cannabis use. While these studies focused on non-affective psychotic disorders, it is possible that the same genetic factors that apply to non-affective psychosis may be at play for affective psychotic disorders, given the moderating effects observed by gender.

Lastly, although findings among males were not statistically significant, the difference in cannabis use rates observed among males with ADPF may be clinically relevant. This finding may inform clinical practice and be important to keep in mind for care planning for treating individuals with AD with psychotic symptoms and reporting cannabis use prior to admission. If continued, cannabis use predicts poorer mental health outcomes, such as greater chances of relapsing in psychotic episodes, a longer length of stay and experiencing greater severity of psychotic symptoms.(108) One recommendation for future research would

be to longitudinally study the impact on mental health and hospital outcomes (e.g. readmission) among those who continue to use cannabis throughout the course of their mental illness.

In this study, females with affective psychotic disorders may be at a lower risk of engaging in frequent cannabis use compared to males, and therefore, a protective effect was observed against using cannabis prior to hospitalization. The RAI-MH however currently does not capture data distinguishing between sex assigned at birth and gender identity separately. Thus, the study was unable to differentiate between patients who identified with the gender assigned at birth or otherwise. The lack of data on gender and sex is an important limitation to consider, and conclusions regarding the underlying biological mechanisms between the sexes cannot be drawn with certainty. Overall, due to this study's exploratory and observational design, findings must be interpreted with caution.

Further investigation is required, including qualitative study designs, to understand why men and women with MDD and BD use cannabis and whether other factors at play (e.g. social determinants of health) influence people's motives for substance use. Research focusing on gender and sex is needed to understand better the motivations for use, and biological mechanisms between males and females in relation to cannabis exposure and the risk of experiencing affective psychotic disorders. For instance, it is possible that patients with ADPF could either be using cannabis to self-medicate for affective or psychotic symptoms, or whether other reasons for cannabis use are promoting first onset or the exacerbation of mental health symptoms leading to hospitalization. It is recommended that prospective studies be conducted to parse apart the direction of the association, as well.

Age did not modify the association between ADPF and cannabis use. Cannabis is a commonly-used substance in the general population, especially among young adults.(15) Among inpatient psychiatric populations, cannabis is even more commonly-used than in the general population across all age groups.(15,24) Differences between ADPF may have been difficult to discern because our sample was comprised of a clinical population. Using OMHRS data, McGuckin et al.'s(24) study found that 26% of inpatient psychiatric patients reported cannabis use 30 days prior to first admission in 2017 in Ontario, with about 40% of patients under the age of 34 reporting cannabis use within 30 days of admission. In contrast, the overall prevalence of past-year cannabis use in the general population of Ontario was found to be 14% in 2017.(15) Due to high prevalence rates in inpatient psychiatry, differences in cannabis use prior to admission between the psychotic and non-psychotic AD groups may not have been discernable as cannabis use is especially common among younger age groups regardless of diagnosis.(16,24)

Furthermore, cannabis use was found to be particularly common among younger age groups in our sample as 18–24-year-olds reported the highest rates of past 30-day use. Interestingly, the 18–24-year-old and 35-44-year-old age groups demonstrated the greatest differences in rates of cannabis exposure compared to all other ages between AD with and without psychotic features. The incidence of first-onset psychosis typically occurs in younger age groups, including those with affective psychotic disorders,(109,110) and heavy use is associated with earlier onset of non-affective psychotic disorder.(35,39) It is possible that the trends in higher rates of cannabis use among 18-24 and 35-44 year-olds is capturing some of those who are experiencing first onset of affective psychotic disorder in addition to the influence of frequent cannabis use prior to admission. While the RAI-MH does not include follow-up questions regarding frequency and dosage of substance use, such information could provide further insight into the effects of age on cannabis consumption and affective psychotic disorders. For example, would the risk of affective psychosis be the same among young adults who are frequent users of high-potency cannabis compared to older demographics with the same frequency and dosages of use? Research conducted among clinical and general populations is needed to discern the differences between cannabis use and ADPF by age groups to identify whether the same trends exist for affective psychotic disorders.

6.1 Strengths and Limitations

The study has some strengths. In examining associations between AD and cannabis exposure, the analysis adjusted for a range of covariates beyond demographics and diagnostics. For instance, the inclusion of a range of other substances used 30 days prior to admission was used to account for the potential impact of other substance use on the association between ADPF and cannabis, rather than substance use diagnosis. Adjustment for diagnosis alone may have resulted in under adjustment because not everyone using substances would have had a substance use diagnosis but may have an elevated likelihood of having used cannabis.(24) Secondly, a strength of the data source used is that it captures all patients admitted to inpatient psychiatry in Ontario. Complete capture of the data enables the findings of this study to be generalizable to inpatient psychiatric contexts in the province at a population level.

Finally, the comprehensive data used for this study can also be useful for future studies in examining how various clinical symptoms may be related to the use of cannabis prior to admission. The dichotomous approach of using diagnostic categories may have been limiting by excluding individuals who did not meet certain criteria to receive a formal AD diagnosis with psychotic features even though they may be experiencing psychotic symptoms. Alternatively, future research can undertake a combined approach,

where both diagnostic and symptom-based indicators of psychosis can be used to explore the association between cannabis use and psychosis among those with affective psychotic disorders. A combined approach may capture a more comprehensive sample of individuals impacted by cannabis use, rather than solely investigating psychotic symptoms or solely looking at a diagnosis of psychotic features among those with AD. The PSS embedded within OMHRS measures the frequency of hallucinations, delusions, and abnormal thoughts.(96) In this study, the proportion of those with a PSS score (32.5%) above 1 among those without ADPF indicates that psychotic symptoms were present. regardless of diagnosis. For example, one study on childhood trauma, cannabis use and psychosis among those with BD used a combined approach and found support for looking at dimensional and dichotomous approaches for exploring the etiology of psychosis among those with BD. Research on combined approaches is ongoing. More recently, studies have found support for using combined approaches in studying the etiology of psychotic disorders and informing effective care planning.(111,112)

There are several limitations to the study. Cannabis use is likely to be predominantly self-reported, which introduces the possibility of patients underreporting cannabis use behaviour due to social desirability and recall bias. The time period of the study overlaps with the legalization of recreational cannabis use in Canada. Recreational cannabis use in Canada was legalized on October 17th, 2018.(113) Individuals may have previously hesitated to report substance use behaviour due to their illicit status pre-legalization and a fear of facing repercussions. Post-legalization, patients may have been less hesitant to report cannabis use, and therefore, this policy change could have contributed to the increase in reports observed in the study sample. The binary logistic regression models (Models 2-6) included year as a covariate to account for differences in cannabis use and reporting overtime to control for the potential impact of legalization on self-reported cannabis use. Furthermore, the presence of telescoping bias is important to consider. Telescoping bias refers to respondents reporting an event occurring earlier or later than the time the event occurred.(114) Individuals may falsely recall the number of days prior to hospitalization when they consumed cannabis leading to the underreporting or overestimating past-month use. Patients may incorrectly recall and report cannabis use within 30 days of admission even though the true time of use may have been over 30 days prior to admission. This may have led to the overestimation of the proportion of cannabis users vs non-users in the sample. Conversely, individuals may falsely recall that they used cannabis over 30 days of admission when they truly used cannabis within 30 days prior to hospitalization, which may have led to the underestimation of the time of cannabis use. In addition to observing and talking with patients, clinicians also consult with other informants, such as family

members, friends or others providing formal care to the patient in the process of administering the RAI-MH assessment. It is not possible to determine if cannabis use was self-reported or reported by another informant. However, using multiple sources of informants may have mitigated the effects of self-report bias on the study.(2) Another limitation of the study to consider was the lack of information on reasons for cannabis use, such as whether a patient is using cannabis recreationally or medically. Currently, the RAI-MH does not include an indicator regarding reasons for cannabis use. Some use medical cannabis to relieve chronic pain associated with various health conditions (e.g. cancer, musculoskeletal conditions, and neuropathic pain) or as a sleep aid in addition to mental health conditions such as, anxiety and depression.(12,68,103–105) The groups for AD with and without features can be comprised of a proportion of individuals cannabis therapeutically, and this study was unable to differentiate between individuals who used cannabis for recreational or medical reasons and assess whether the association varied by reasons for use or control for it. Information on reasons for use could have added further context to the association observed between cannabis use and affective disorders by gender.

Secondly, there are limitations to the way in which data on cannabis use are captured. The substance use indicator, which includes cannabis use, only captures when an individual used cannabis prior to admission. It does not capture frequency, type (CBD vs THC vs hybrid) or potency of cannabis product used. The cannabis use indicator may have been limited in its ability to identify frequent users without the availability of other indicators based on frequency, dosage, and type of product (THC/CBD-based). However, past-month cannabis use is correlated with frequent use among the general Canadian population, thus, the item is a proxy method of capturing frequent users.(4)

Next, the data were not representative of the general population, or the entire population of persons with AD, as the data were only collected from individuals admitted to an acute care setting. Patients exhibiting psychotic symptoms and with substance use may have more likely than those without psychosis or substance use to be admitted to an inpatient psychiatric bed. Psychiatric patients presenting with lower severity of psychiatric symptoms may have been assigned to medical beds due to the limited availability of psychiatric beds. OMHRS does not capture data from medical beds, and therefore, not all cases of psychiatric admissions were captured. The data captured the most severe cases of individuals with the greatest need for intervention. The conclusions of this study can be generalizable to other acute inpatient psychiatric populations. Future research may further explore the impact of cannabis use among those receiving care through community mental health services.

Finally, the aggregation of mood disorders, MDD and BD with psychotic features, into one diagnostic group may have decreased the sensitivity in detecting specific relationships between psychotic features and cannabis use. Although, other studies have undertaken a similar methodology of grouping together the AD groups.(62,94,115) It is still possible that the grouping of the two mood disorders may have nullified findings if either were inversely associated with cannabis use 30 days prior to admission to inpatient psychiatry.

6.2 Implications for Future Research, Policy, and Practice:

This research has added new insights into the relationship between affective psychotic disorders and cannabis that are important for promoting future research. As previously discussed, there is a need for more research on specific diagnoses or dimensions of affective psychotic disorders with prospective study designs and the use of cannabis use indicators measuring frequency and dosages of product types. To elaborate, a causal link cannot be established between cannabis use and affective psychotic disorders as the study is cross-sectional in design. Studies with longitudinal designs which preserve temporality between exposure and outcome are needed. Furthermore, another area of future research would be to investigate biological mechanisms that could potentially identify and explain the underlying reasons for the association between cannabis and psychotic symptoms, with particular attention to gender and sex-based differences. Research is also needed around BD and MDD with psychotic features due to the limited literature on affective psychotic disorders. This would aid in establishing underlying mechanisms that are common among psychotic disorders in relation to the dose-response effects of cannabis use. In assessing gender differences, studies also need to consider and distinguish between gender and sex. The RAI-MH captures only the gender identities of individuals admitted to inpatient psychiatry. Individuals of non-binary identities may choose not to disclose their assigned sex at birth at the time of psychiatric assessment. It is important to recognize differences in gender beyond binary experiences. Those identifying as transgender and non-binary have been shown to have significantly different, often poorer mental health symptoms and are more likely to be denied health care services than cisgender men, which indicates a greater and more specialized need for health services in this population.(116) Lastly, further investigation is needed on the impact of various potencies, strains, and frequencies of cannabis use on individuals with affective psychotic disorders. In the Canadian context, cannabis regulations vary from province to province, which could provide an opportunity to identify the public health impacts of regulatory changes on the general population.

There are important public health policy implications of this research for harm reduction initiatives. There is an ongoing need for education about cannabis use targeted towards youth and persons at risk of experiencing mental health issues. While the specific role of cannabis on AD among the study sample is unknown, the proportion reporting use of cannabis was high, particularly among younger patients. While Canada already uses plain packaging of cannabis products that include warnings regarding the increased risk of experiencing psychosis associated with frequent use(117), further evaluation of warning labels specific to mental health may be warranted. Ongoing educational efforts for youth and the public are important to consider given the common use of cannabis, including for medical use. In recent studies, Canadian youth and young adults who have reported cannabis use for medical purposes also reported using it to address mental health concerns.(118,119) This highlights potential unmet mental health needs among these populations and calls for a greater need to understand why people engage in substance use. Furthermore, among participants in surveys on cannabis consumption, the majority of those who reported past-year use of cannabis for medical purposes did not do so by attaining medical documentation through a healthcare provider.(5,118) Persons who use cannabis may hesitate to approach health care providers out of concerns for facing judgement and lacking support from clinicians.(120) There is a need for encouraging discussions between healthcare providers and patients to understand patients' motivations for cannabis use, discuss potential care plans for mental health concerns, and reduce harm among heavy users who are predisposed to serious mental illness in particular. Lastly, identifying gender-based patterns can inform clinical practice where healthcare providers may use this information to identify groups that are at greatest risk of using cannabis in addition to other risk factors and can facilitate discussion among males surrounding frequent use of high-potency cannabis use. Beyond individual-level factors, it is important to gain an understanding of systemic or social factors that contribute to substance use to produce effective harm reduction interventions and cannabis policies.(121)

7. Conclusion:

In addressing gaps in the literature regarding cannabis use and affective psychotic disorders, study results demonstrated a nuanced relationship between affective psychotic disorders and cannabis use. Gender was found to moderate the likelihood of having used cannabis 30 days prior to admission to inpatient psychiatry among those with ADPF compared to individuals without ADPF. Females with ADPF were found to be at lower odds of using cannabis before hospitalization compared to females without ADPF. The association was neither significant among males nor was age a moderator in the odds of using cannabis and ADPF. Based on these findings, the study has implications for informing early intervention initiatives for harm reduction and facilitating discussions regarding cannabis use among persons with severe mental health concerns. Future research with longitudinal study designs should continue investigating the relationship between cannabis product types, potencies, and frequencies of use among those with ADPF by gender and age groups.

References

1. World Drug Report 2020. 2020.
2. ElSohly MA, Slade D. Chemical constituents of marijuana: The complex mixture of natural cannabinoids. Life Sci [Internet]. 2005 Dec 22 [cited 2020 Oct 4];78(5):539–48. Available from: https://pubmed.ncbi.nlm.nih.gov/16199061/
3. Atakan Z. Cannabis, a complex plant: Different compounds and different effects on individuals [Internet]. Vol. 2, Therapeutic Advances in Psychopharmacology. SAGE PublicationsSage UK: London, England; 2012 [cited 2021 Jan 10]. p. 241–54. Available from: http://journals.sagepub.com/doi/10.1177/2045125312457586
4. Goodman S, Wadsworth E, Leos-Toro C, Hammond D. Prevalence and forms of cannabis use in legal vs. illegal recreational cannabis markets. Int J Drug Policy. 2020 Feb 1;76:102658.
5. Canadian Cannabis Survey 2019 - Summary . 2019.
6. Cascini F, Aiello C, Tanna G Di. Increasing Delta-9-Tetrahydrocannabinol (-9-THC) Content in Herbal Cannabis Over Time: Systematic Review and Meta-Analysis [Internet]. Vol. 5, Current Drug Abuse Reviews. 2012 [cited 2020 Dec 29]. Available from: http://www.unodc.org/unodc/en/data-and-analysis/WDR-
7. ElSohly MA, Mehmedic Z, Foster S, Gon C, Chandra S, Church JC. Changes in cannabis potency over the last 2 decades (1995-2014): Analysis of current data in the United States. Biol Psychiatry [Internet]. 2016 [cited 2020 Dec 29];79(7):613–9. Available from: https://pubmed.ncbi.nlm.nih.gov/26903403/
8. Freeman TP, Groshkova T, Cunningham A, Sedefov R, Griffiths P, Lynskey MT. Increasing potency and price of cannabis in Europe, 2006-16. Addiction [Internet]. 2019 Jun 1 [cited 2020 Dec 29];114(6):1015–23. Available from: http://doi.wiley.com/10.1111/add.14525
9. Chandra S, Radwan MM, Majumdar CG, Church JC, Freeman TP, ElSohly MA. New trends in cannabis potency in USA and Europe during the last decade (2008–2017). Eur Arch Psychiatry Clin Neurosci [Internet]. 2019 Feb 1 [cited 2020 Dec 29];269(1):5–15. Available from: https://doi.org/10.1007/s00406-019-00983-5
10. Mahamad S, Wadsworth E, Rynard V, Goodman S, Hammond D. Availability, retail price and potency of legal and illegal cannabis in Canada after recreational cannabis legalisation. Drug Alcohol Rev [Internet]. 2020 May 14 [cited 2020 Dec 29];39(4):337–46. Available from:

https://onlinelibrary.wiley.com/doi/abs/10.1111/dar.13069

11. Volkow ND, Baler RD, Compton WM, Weiss SRB. Adverse Health Effects of Marijuana Use. N Engl J Med [Internet]. 2014 Jun 5 [cited 2020 Dec 29];370(23):2219–27. Available from: https://www.nejm.org/doi/full/10.1056/nejmra1402309
12. Walsh Z, Callaway R, Belle-Isle L, Capler R, Kay R, Lucas P, et al. Cannabis for therapeutic purposes: Patient characteristics, access, and reasons for use. Int J Drug Policy. 2013 Nov 1;24(6):511–6.
13. Fusar-Poli P, Tantardini M, De Simone S, Ramella-Cravaro V, Oliver D, Kingdon J, et al. Deconstructing vulnerability for psychosis: Meta-analysis of environmental risk factors for psychosis in subjects at ultra high-risk [Internet]. Vol. 40, European Psychiatry. Cambridge University Press; 2017 [cited 2020 Nov 11]. p. 65–75. Available from: https://pubmed-ncbi-nlm-nih-gov.proxy.lib.uwaterloo.ca/27992836/
14. Archie S, Boydell KM, Stasiulis E, Volpe T, Gladstone BM. Reflections of young people who have had a first episode of psychosis: what attracted them to use alcohol and illicit drugs? Early Interv Psychiatry [Internet]. 2013 May 1 [cited 2020 Dec 29];7(2):193–9. Available from: http://doi.wiley.com/10.1111/j.1751-7893.2012.00355.x
15. Rotermann M. Analysis of trends in the prevalence of cannabis use and related metrics in Canada. Heal Reports. 2019 Jun 1;30(6):3–13.
16. Maloney-Hall B, Wallingford SC, Konefal S, Young MM. Psychotic disorder and cannabis use: Canadian hospitalization trends, 2006–2015. Heal Promot Chronic Dis Prev Canada [Internet]. 2020 May 1 [cited 2020 Dec 29];40(5–6):176–83. Available from: https://doi.org/10.24095/hpcdp.40.5/6.06
17. Lu HC, MacKie K. An introduction to the endogenous cannabinoid system [Internet]. Vol. 79, Biological Psychiatry. Elsevier USA; 2016 [cited 2020 Dec 29]. p. 516–25. Available from: /pmc/articles/PMC4789136/?report=abstract
18. Volkow ND, Hampson AJ, Baler RD. Don't Worry, Be Happy: Endocannabinoids and Cannabis at the Intersection of Stress and Reward. Annu Rev Pharmacol Toxicol [Internet]. 2017 Jan 6 [cited 2020 Dec 29];57(1):285–308. Available from: http://www.annualreviews.org/doi/10.1146/annurev-pharmtox-010716-104615
19. Zou S, Kumar U. Cannabinoid receptors and the endocannabinoid system: Signaling and function in the central nervous system [Internet]. Vol. 19, International Journal of Molecular Sciences.

MDPI AG; 2018 [cited 2020 Dec 29]. Available from: /pmc/articles/PMC5877694/?report=abstract

20. Kilaru A, Chapma KD. The endocannabinoid system [Internet]. Vol. 64, Essays in Biochemistry. Portland Press Ltd; 2020 [cited 2020 Dec 29]. p. 485–99. Available from: https://pubmed.ncbi.nlm.nih.gov/32648908/
21. Volkow ND, Hampson AJ, Baler RD. Don't Worry, Be Happy: Endocannabinoids and Cannabis at the Intersection of Stress and Reward. Annu Rev Pharmacol Toxicol. 2017 Jan 6;57(1):285–308.
22. D'Souza DC, Cortes-Briones JA, Ranganathan M, Thurnauer H, Creatura G, Surti T, et al. Rapid Changes in Cannabinoid 1 Receptor Availability in Cannabis-Dependent Male Subjects after Abstinence from Cannabis. Biol Psychiatry Cogn Neurosci Neuroimaging [Internet]. 2016 Jan 1 [cited 2020 Dec 29];1(1):60–7. Available from: /pmc/articles/PMC4742341/?report=abstract
23. Hirvonen J, Goodwin RS, Li CT, Terry GE, Zoghbi SS, Morse C, et al. Reversible and regionally selective downregulation of brain cannabinoid CB 1 receptors in chronic daily cannabis smokers. Mol Psychiatry [Internet]. 2012 Jun [cited 2020 Dec 29];17(6):642–9. Available from: /pmc/articles/PMC3223558/?report=abstract
24. McGuckin T, Ferro MA, Hammond D, Stewart S, Maloney-Hall B, Madi N, et al. How High? Trends in Cannabis Use Prior to First Admission to Inpatient Psychiatry in Ontario, Canada, between 2007 and 2017: À quelle hauteur? Les tendances de l'usage du cannabis avant la première hospitalisation en psychiatrie en Ontario, Canada entre 2007 et 2017. Can J Psychiatry [Internet]. 2020 Dec 31 [cited 2021 Nov 28];706743720984679. Available from: http://www.ncbi.nlm.nih.gov/pubmed/33380219
25. Bromley S, Reg Monica Choi O, Sabiha Faruqui F. First episode psychosis An information guide revised edition [Internet]. 1999 [cited 2020 Nov 28]. Available from: www.camh.ca
26. McCutcheon RA, Reis Marques T, Howes OD. Schizophrenia - An Overview [Internet]. Vol. 77, JAMA Psychiatry. American Medical Association; 2020 [cited 2020 Dec 29]. p. 201–10. Available from: https://pubmed.ncbi.nlm.nih.gov/31664453/
27. Lichtenstein P, Yip BH, Björk C, Pawitan Y, Cannon TD, Sullivan PF, et al. Common genetic influences for schizophrenia and bipolar disorder: A population-based study of 2 million nuclear families.
28. Hilker R, Helenius D, Fagerlund B, Skytthe A, Christensen K, Werge TM, et al. Heritability of

Schizophrenia and Schizophrenia Spectrum Based on the Nationwide Danish Twin Register. Biol Psychiatry. 2018 Mar 15;83(6):492–8.

29. Sullivan PF, Kendler KS, Neale MC. Schizophrenia as a Complex Trait: Evidence from a Meta-analysis of Twin Studies. Arch Gen Psychiatry. 2003 Dec;60(12):1187–92.
30. LE L, R K, B M, MJ G. Risk of schizophrenia in relatives of individuals affected by schizophrenia: A meta-analysis. Psychiatry Res. 2020 Apr 1;286:112852.
31. Davies C, Segre G, Estradé A, Radua J, De Micheli A, Provenzani U, et al. Prenatal and perinatal risk and protective factors for psychosis: a systematic review and meta-analysis. The Lancet Psychiatry. 2020;7(5).
32. Bolhuis K, Kushner SA, Yalniz S, Hillegers MHJ, Jaddoe VWV, Tiemeier H, et al. Maternal and paternal cannabis use during pregnancy and the risk of psychotic-like experiences in the offspring. Schizophr Res. 2018 Dec 1;202:322–7.
33. McHugh MJ, McGorry PD, Yuen HP, Hickie IB, Thompson A, de Haan L, et al. The Ultra-High-Risk for psychosis groups: Evidence to maintain the status quo. Schizophr Res. 2018 May 1;195:543–8.
34. Carney R, Cotter J, Firth J, Bradshaw T, Yung AR. Cannabis use and symptom severity in individuals at ultra high risk for psychosis: a meta-analysis. Acta Psychiatr Scand [Internet]. 2017 Jul 1 [cited 2020 Dec 29];136(1):5–15. Available from: http://doi.wiley.com/10.1111/acps.12699
35. Hamilton I. Cannabis, psychosis and schizophrenia: unravelling a complex interaction. Addiction [Internet]. 2017 Sep 1 [cited 2020 Dec 29];112(9):1653–7. Available from: https://onlinelibrary.wiley.com/doi/full/10.1111/add.13826%4010.1111/%28ISSN%291360-0443.addiction_classics_virtual_issue
36. D'Souza DC, Sewell RA, Ranganathan M. Cannabis and psychosis/schizophrenia: Human studies [Internet]. Vol. 259, European Archives of Psychiatry and Clinical Neuroscience. NIH Public Access; 2009 [cited 2020 Dec 29]. p. 413–31. Available from: /pmc/articles/PMC2864503/?report=abstract
37. Marconi A, Di Forti M, Lewis CM, Murray RM, Vassos E. Meta-analysis of the Association Between the Level of Cannabis Use and Risk of Psychosis. Schizophr Bull [Internet]. 2016 Sep 1 [cited 2021 Jan 4];42(5):1262–9. Available from: https://academic.oup.com/schizophreniabulletin/article-lookup/doi/10.1093/schbul/sbw003
38. Di Forti M, Marconi A, Carra E, Fraietta S, Trotta A, Bonomo M, et al. Proportion of patients in

south London with first-episode psychosis attributable to use of high potency cannabis: A case-control study. The Lancet Psychiatry. 2015 Mar 1;2(3):233–8.

39. Di Forti M, Sallis H, Allegri F, Trotta A, Ferraro L, Stilo SA, et al. Daily Use, Especially of High-Potency Cannabis, Drives the Earlier Onset of Psychosis in Cannabis Users. Schizophr Bull [Internet]. 2014 Nov 1 [cited 2020 Dec 29];40(6):1509–17. Available from: https://academic.oup.com/schizophreniabulletin/article-lookup/doi/10.1093/schbul/sbt181
40. van der Steur SJ, Batalla A, Bossong MG. Factors Moderating the Association between Cannabis Use and Psychosis Risk: A Systematic Review. Brain Sci [Internet]. 2020 Feb 12 [cited 2020 Dec 29];10(2):97. Available from: https://www.mdpi.com/2076-3425/10/2/97
41. Dekker N, Meijer J, Koeter M, Van Den Brink W, Van Beveren N, Kahn RS, et al. Age at onset of non-affective psychosis in relation to cannabis use, other drug use and gender. Psychol Med. 2012 Sep;42(9):1903–11.
42. Decoster J, van Os J, Kenis G, Henquet C, Peuskens J, De Hert M, et al. Age at onset of psychotic disorder: Cannabis, BDNF Val66Met, and sex-specific models of gene-environment interaction. Am J Med Genet Part B Neuropsychiatr Genet [Internet]. 2011 Apr 1 [cited 2020 Dec 29];156(3):363–9. Available from: http://doi.wiley.com/10.1002/ajmg.b.31174
43. Forti M Di, Quattrone D, Freeman TP, Tripoli G, Gayer-Anderson C, Quigley H, et al. The contribution of cannabis use to variation in the incidence of psychotic disorder across Europe (EU-GEI): a multicentre case-control study. 2019 [cited 2020 Dec 29];427. Available from: http://dx.doi.org/10.1016/
44. Belbasis L, Köhler CA, Stefanis N, Stubbs B, van Os J, Vieta E, et al. Risk factors and peripheral biomarkers for schizophrenia spectrum disorders: an umbrella review of meta-analyses. Acta Psychiatr Scand [Internet]. 2018 Feb 1 [cited 2021 Jan 4];137(2):88–97. Available from: http://doi.wiley.com/10.1111/acps.12847
45. Arranz S, Monferrer N, Jose Algora M, Cabezas A, Sole M, Vilella E, et al. The relationship between the level of exposure to stress factors and cannabis in recent onset psychosis. Schizophr Res. 2018 Nov 1;201:352–9.
46. Pauselli L, Birnbaum ML, Vázquez Jaime BP, Paolini E, Kelley ME, Broussard B, et al. Demographic and socioenvironmental predictors of premorbid marijuana use among patients with first-episode psychosis. Schizophr Res. 2018 Jul 1;197:544–9.
47. Karcher NR, Barch DM, Demers CH, Baranger DAA, Heath AC, Lynskey MT, et al. Genetic

Predisposition vs Individual-Specific Processes in the Association between Psychotic-like Experiences and Cannabis Use. JAMA Psychiatry [Internet]. 2019 Jan 1 [cited 2020 Dec 29];76(1):87–94. Available from: https://pubmed.ncbi.nlm.nih.gov/30347017/

48. Mané A, Bergé D, Penzol MJ, Parellada M, Bioque M, Lobo A, et al. Cannabis use, COMT, BDNF and age at first-episode psychosis. Psychiatry Res [Internet]. 2017 Apr 1 [cited 2020 Nov 29];250:38–43. Available from: https://pubmed.ncbi.nlm.nih.gov/28142064/
49. Vaucher J, Keating BJ, Lasserre AM, Gan W, Lyall DM, Ward J, et al. Cannabis use and risk of schizophrenia: A Mendelian randomization study. Mol Psychiatry [Internet]. 2018 May 1 [cited 2020 Sep 25];23(5):1287–92. Available from: https://pubmed.ncbi.nlm.nih.gov/28115737/
50. Gage SH, Jones HJ, Burgess S, Bowden J, Davey Smith G, Zammit S, et al. Assessing causality in associations between cannabis use and schizophrenia risk: A two-sample Mendelian randomization study. Psychol Med [Internet]. 2017 Apr 1 [cited 2020 Dec 29];47(5):971–80. Available from: https://pubmed.ncbi.nlm.nih.gov/27928975/
51. Pasman JA, Verweij KJH, Gerring Z, Stringer S, Sanchez-Roige S, Treur JL, et al. GWAS of lifetime cannabis use reveals new risk loci, genetic overlap with psychiatric traits, and a causal influence of schizophrenia. Nat Neurosci [Internet]. 2018 Sep 1 [cited 2021 Jan 12];21(9):1161–70. Available from: https://doi.org/10.1038/s41593-018-0206-1
52. Belmaker RH, Agam G. Major Depressive Disorder. N Engl J Med [Internet]. 2008 Jan 3 [cited 2022 Jan 10];358(1):55–68. Available from: http://www.nejm.org/doi/abs/10.1056/NEJMra073096
53. Knoll AD, MacLennan RN. Prevalence and correlates of depression in Canada: Findings from the Canadian Community Health Survey. Can Psychol [Internet]. 2017 May 1 [cited 2021 Nov 29];58(2):116–23. Available from: /record/2017-12017-001
54. Hasin DS, Sarvet AL, Meyers JL, Saha TD, Ruan WJ, Stohl M, et al. Epidemiology of adult DSM-5 major depressive disorder and its specifiers in the United States. JAMA Psychiatry [Internet]. 2018 Apr 1 [cited 2021 Nov 29];75(4):336–46. Available from: https://jamanetwork.com/
55. Patten SB, Williams JVA, Lavorato DH, Wang JL, McDonald K, Bulloch AGM. Descriptive epidemiology of major depressive disorder in Canada in 2012. Can J Psychiatry [Internet]. 2015 Jan 1 [cited 2022 Jan 19];60(1):23–30. Available from: https://pubmed.ncbi.nlm.nih.gov/25886546/

56. Gorfinkel LR, Stohl M, Hasin D. Association of Depression with Past-Month Cannabis Use among US Adults Aged 20 to 59 Years, 2005 to 2016. JAMA Netw Open [Internet]. 2020 Aug 18 [cited 2022 Jan 19];3(8). Available from: /pmc/articles/PMC7435337/
57. Halladay JE, Munn C, Boyle M, Jack SM, Georgiades K. Temporal Changes in the Cross-Sectional Associations between Cannabis Use, Suicidal Ideation, and Depression in a Nationally Representative Sample of Canadian Adults in 2012 Compared to 2002. Can J Psychiatry [Internet]. 2020 Feb 1 [cited 2022 Jan 19];65(2):115–23. Available from: https://pubmed.ncbi.nlm.nih.gov/31177831/
58. Lev-Ran S, Roerecke M, Le Foll B, George TP, McKenzie K, Rehm J. The association between cannabis use and depression: A systematic review and meta-analysis of longitudinal studies. Psychol Med [Internet]. 2014 [cited 2021 Nov 29];44(4):797–810. Available from: https://www.cambridge.org/core/journals/psychological-medicine/article/abs/association-between-cannabis-use-and-depression-a-systematic-review-and-metaanalysis-of-longitudinal-studies/B144B7AE5A3D973289DBDD99ADE21E58
59. Schoeler T, Theobald D, Pingault JB, Farrington DP, Coid JW, Bhattacharyya S. Developmental sensitivity to cannabis use patterns and risk for major depressive disorder in mid-life: Findings from 40 years of follow-up. Psychol Med [Internet]. 2018 Oct 1 [cited 2022 Jan 19];48(13):2169–76. Available from: https://www.cambridge.org/core/journals/psychological-medicine/article/abs/developmental-sensitivity-to-cannabis-use-patterns-and-risk-for-major-depressive-disorder-in-midlife-findings-from-40-years-of-followup/6EF430A97C29BD11E0CD0678390AA432
60. Gukasyan N, Strain EC. Relationship between cannabis use frequency and major depressive disorder in adolescents: Findings from the National Survey on Drug Use and Health 2012–2017. Drug Alcohol Depend. 2020 Mar 1;208:107867.
61. Danielsson AK, Lundin A, Agardh E, Allebeck P, Forsell Y. Cannabis use, depression and anxiety: A 3-year prospective population-based study. J Affect Disord. 2016 Mar 15;193:103–8.
62. Manrique-Garcia E, Zammit S, Dalman C, Hemmingsson T, Andreasson S, Allebeck P. Cannabis, schizophrenia and other non-affective psychoses: 35 years of follow-up of a population-based cohort. Psychol Med [Internet]. 2012 Jun [cited 2020 Dec 29];42(6):1321–8. Available from: https://www.cambridge.org/core/journals/psychological-medicine/article/abs/cannabis-schizophrenia-and-other-nonaffective-psychoses-35-years-of-followup-of-a-populationbased-

cohort/D4A7F9409437E308002E1EA85F4EF319

63. Feingold D, Rehm J, Lev-Ran S. Cannabis use and the course and outcome of major depressive disorder: A population based longitudinal study. Psychiatry Res. 2017 May 1;251:225–34.

64. Horwood LJ, Fergusson DM, Coffey C, Patton GC, Tait R, Smart D, et al. Cannabis and depression: An integrative data analysis of four Australasian cohorts. Drug Alcohol Depend [Internet]. 2012 Dec 1 [cited 2022 Jan 19];126(3):369–78. Available from: https://pubmed.ncbi.nlm.nih.gov/22749560/

65. Hengartner MP, Angst J, Ajdacic-Gross V, Rössler W. Cannabis use during adolescence and the occurrence of depression, suicidality and anxiety disorder across adulthood: Findings from a longitudinal cohort study over 30 years. J Affect Disord [Internet]. 2020 Jul 1 [cited 2022 Jan 19];272:98–103. Available from: https://pubmed.ncbi.nlm.nih.gov/32379627/

66. Blest-Hopley G, Colizzi M, Giampietro V, Bhattacharyya S. Is the Adolescent Brain at Greater Vulnerability to the Effects of Cannabis? A Narrative Review of the Evidence. Vol. 11, Frontiers in Psychiatry. Frontiers Media S.A.; 2020. p. 859.

67. Kozak K, H. Smith P, Lowe DJ., Weinberger AH, Cooper ZD, Rabin RA, et al. A systematic review and meta-analysis of sex differences in cannabis use disorder amongst people with comorbid mental illness. Am J Drug Alcohol Abuse [Internet]. 2021 Sep 3 [cited 2021 Nov 29];47(5):535–47. Available from: https://www.tandfonline.com/doi/full/10.1080/00952990.2021.1946071

68. Kosiba JD, Maisto SA, Ditre JW. Patient-reported use of medical cannabis for pain, anxiety, and depression symptoms: Systematic review and meta-analysis. 2019 [cited 2022 Jan 5]; Available from: https://doi.org/10.1016/j.socscimed.2019.06.005

69. Bahorik AL, Leibowitz A, Sterling SA, Travis A, Weisner C, Satre DD. Patterns of marijuana use among psychiatry patients with depression and its impact on recovery. J Affect Disord. 2017 Apr 15;213:168–71.

70. Hser YI, Mooney LJ, Huang D, Zhu Y, Tomko RL, McClure E, et al. Reductions in cannabis use are associated with improvements in anxiety, depression, and sleep quality, but not quality of life. J Subst Abuse Treat [Internet]. 2017 Oct 1 [cited 2022 Jan 19];81:53–8. Available from: https://pubmed.ncbi.nlm.nih.gov/28847455/

71. Moitra E, Anderson BJ, Stein MD. Reductions in cannabis use are associated with mood improvement in female emerging adults. Depress Anxiety [Internet]. 2016 Apr 1 [cited 2022 Jan

19];33(4):332–8. Available from: https://onlinelibrary.wiley.com/doi/10.1002/da.22460

72. Merikangas KR, Jin R, He JP, Kessler RC, Lee S, Sampson NA, et al. Prevalence and correlates of bipolar spectrum disorder in the World Mental Health Survey Initiative. Arch Gen Psychiatry [Internet]. 2011 Mar 1 [cited 2021 Nov 29];68(3):241–51. Available from: http://archpsyc.ama-assn.org/cgi/content/full/68/3/241
73. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. Fifth Edit. Washington, DC: American Psychiatric Association; 2013.
74. McDonald KC, Bulloch AGM, Duffy A, Bresee L, Williams JVA, Lavorato DH, et al. Prevalence of bipolar I and II disorder in Canada. Can J Psychiatry [Internet]. 2015 Mar 1 [cited 2022 Jan 9];60(3):151–6. Available from: /pmc/articles/PMC4394715/
75. Bahji A, Danilewitz M, Vazquez G, Patten S. The Prevalence of Cannabis Use Disorder Comorbidity in Individuals With Bipolar Disorder: A Systematic Review and Meta-Analysis. Can J Addict [Internet]. 2021 Sep [cited 2022 Jan 12];12(3):22–38. Available from: https://journals.lww.com/10.1097/CXA.0000000000000123
76. Bolton S, Warner J, Harriss E, Geddes J, Saunders KEA. Bipolar disorder: Trimodal age-at-onset distribution [Internet]. Vol. 23, Bipolar Disorders. John Wiley and Sons Inc; 2021 [cited 2022 Jan 19]. p. 341–56. Available from: https://pubmed.ncbi.nlm.nih.gov/33030292/
77. Pinto JV, Medeiros LS, Santana da Rosa G, Santana de Oliveira CE, Crippa JA de S, Passos IC, et al. The prevalence and clinical correlates of cannabis use and cannabis use disorder among patients with bipolar disorder: A systematic review with meta-analysis and meta-regression. Vol. 101, Neuroscience and Biobehavioral Reviews. Elsevier Ltd; 2019. p. 78–84.
78. Taub S, Feingold D, Rehm J, Lev-Ran S. Patterns of cannabis use and clinical correlates among individuals with Major Depressive Disorder and Bipolar Disorder. Compr Psychiatry. 2018 Jan 1;80:89–96.
79. Weinstock LM, Gaudiano BA, Wenze SJ, Epstein-Lubow G, Miller IW. Demographic and clinical characteristics associated with comorbid cannabis use disorders (CUDs) in hospitalized patients with bipolar i disorder. Compr Psychiatry [Internet]. 2016 Feb 1 [cited 2022 Jan 19];65:57–62. Available from: https://pubmed.ncbi.nlm.nih.gov/26773991/
80. Bartoli F, Crocamo C, Carrà G. Cannabis use disorder and suicide attempts in bipolar disorder: A meta-analysis [Internet]. Vol. 103, Neuroscience and Biobehavioral Reviews. Elsevier Ltd; 2019 [cited 2022 Jan 19]. p. 14–20. Available from: https://pubmed.ncbi.nlm.nih.gov/31121199/

81. Gibbs M, Winsper C, Marwaha S, Gilbert E, Broome M, Singh SP. Cannabis use and mania symptoms: A systematic review and meta-analysis. Vol. 171, Journal of Affective Disorders. Elsevier B.V.; 2015. p. 39–47.
82. Zorrilla I, Aguado J, Haro JM, Barbeito S, López Zurbano S, Ortiz A, et al. Cannabis and bipolar disorder: Does quitting cannabis use during manic/mixed episode improve clinical/functional outcomes? Acta Psychiatr Scand [Internet]. 2015 Feb 1 [cited 2022 Jan 19];131(2):100–10. Available from: https://pubmed.ncbi.nlm.nih.gov/25430820/
83. Kim SW, Dodd S, Berk L, Kulkarni J, De Castella A, Fitzgerald PB, et al. Impact of cannabis use on long-term remission in bipolar I and schizoaffective disorder. Psychiatry Investig [Internet]. 2015 Jul 1 [cited 2022 Jan 10];12(3):349–55. Available from: /pmc/articles/PMC4504917/
84. Lagerberg T V., Icick R, Andreassen OA, Ringen PA, Etain B, Aas M, et al. Cannabis use disorder is associated with greater illness severity in tobacco smoking patients with bipolar disorder. J Affect Disord. 2016 Jan 15;190:286–93.
85. Jefsen OH, Speed M, Speed D, Østergaard SD. Bipolar disorder and cannabis use: A bidirectional two-sample Mendelian randomization study. Addict Biol [Internet]. 2021 Nov 1 [cited 2022 Jan 19];26(6). Available from: https://pubmed.ncbi.nlm.nih.gov/33733564/
86. Perälä J, Suvisaari J, Saarni SI, Kuoppasalmi K, Isometsä E, Pirkola S, et al. Lifetime prevalence of psychotic and bipolar I disorders in a general population. Arch Gen Psychiatry [Internet]. 2007 Jan 1 [cited 2021 Nov 29];64(1):19–28. Available from: https://jamanetwork.com/journals/jamapsychiatry/fullarticle/209973
87. Ohayon MM, Schatzberg AF. Prevalence of depressive episodes with psychotic features in the general population. Am J Psychiatry [Internet]. 2002 Nov 1 [cited 2021 Nov 29];159(11):1855–61. Available from: https://ajp.psychiatryonline.org/doi/abs/10.1176/appi.ajp.159.11.1855
88. Jääskeläinen E, Juola T, Korpela H, Lehtiniemi H, Nietola M, Korkeila J, et al. Epidemiology of psychotic depression - Systematic review and meta-analysis [Internet]. Vol. 48, Psychological Medicine. Cambridge University Press; 2018 [cited 2021 Nov 29]. p. 905–18. Available from: https://www.cambridge.org/core/journals/psychological-medicine/article/abs/epidemiology-of-psychotic-depression-systematic-review-and-metaanalysis/57F7BD26F05E0A4B78A3337C73536813
89. Van Bergen AH, Verkooijen S, Vreeker A, Abramovic L, Hillegers MH, Spijker AT, et al. The characteristics of psychotic features in bipolar disorder. Psychol Med [Internet]. 2019 Sep 1 [cited

2021 Nov 29];49(12):2036–48. Available from: https://www.cambridge.org/core/journals/psychological-medicine/article/abs/characteristics-of-psychotic-features-in-bipolar-disorder/0B66A67B9F8629FCDD65420A389A3C37

90. Dell'Osso B, Camuri G, Cremaschi L, Dobrea C, Buoli M, Ketter TA, et al. Lifetime presence of psychotic symptoms in bipolar disorder is associated with less favorable socio-demographic and certain clinical features. Compr Psychiatry. 2017 Jul 1;76:169–76.
91. Botsford SL, Yang S, George TP. Cannabis and Cannabinoids in Mood and Anxiety Disorders: Impact on Illness Onset and Course, and Assessment of Therapeutic Potential. Am J Addict [Internet]. 2020 Jan 2 [cited 2021 Jan 13];29(1):9–26. Available from: https://onlinelibrary.wiley.com/doi/abs/10.1111/ajad.12963
92. Kvitland LR, Ringen PA, Aminoff SR, Demmo C, Hellvin T, Lagerberg TV, et al. Duration of untreated illness in first-treatment bipolar I disorder in relation to clinical outcome and cannabis use. Psychiatry Res. 2016 Dec 30;246:762–8.
93. Etain B, Lajnef M, Bellivier F, Henry C, M'bailara K, Kahn JP, et al. Revisiting the association between childhood trauma and psychosis in bipolar disorder: A quasi-dimensional path-analysis. J Psychiatr Res. 2017 Jan 1;84:73–9.
94. Mustonen A, Niemelä S, Nordström T, Murray GK, Mäki P, Jääskeläinen E, et al. Adolescent cannabis use, baseline prodromal symptoms and the risk of psychosis. Br J Psychiatry [Internet]. 2018 Apr 1 [cited 2021 Nov 29];212(4):227–33. Available from: http://www.oulu.fi/nfbc/node/
95. Hirdes JP, Smith TF, Rabinowitz T, Yamauchi K, Pérez E, Telegdi NC, et al. The Resident Assessment Instrument-Mental Health (RAI-MH): Inter-Rater Reliability and Convergent Validity. J Behav Heal Serv Res [Internet]. 2002 Nov [cited 2020 Dec 29];29(4):419–32. Available from: https://link.springer.com/article/10.1007/BF02287348
96. Hirdes JP, van Everdingen C, Ferris J, Franco-Martin M, Fries BE, Heikkilä J, et al. The interRAI Suite of Mental Health Assessment Instruments: An Integrated System for the Continuum of Care. Vol. 10, Frontiers in Psychiatry. Frontiers Media S.A.; 2020.
97. Vigod SN, Kurdyak PA, Seitz D, Herrmann N, Fung K, Lin E, et al. READMIT: A clinical risk index to predict 30-day readmission after discharge from acute psychiatric units. J Psychiatr Res. 2015 Feb 1;61:205–13.
98. Perlman CM, Hirdes JP, Vigod S. Psychiatric rehospitalization: Development of a person-level indicator for care planning and quality assurance. Prim Care Companion J Clin Psychiatry

[Internet]. 2015 [cited 2020 Dec 29];17(4). Available from: /pmc/articles/PMC4664575/?report=abstract

99. Martin L, Hirdes JP, Morris JN, Montague P, Rabinowitz T, Fries BE. Validating the Mental Health Assessment Protocols (MHAPs) in the Resident Assessment Instrument Mental Health (RAI-MH). J Psychiatr Ment Health Nurs [Internet]. 2009 Sep 1 [cited 2021 Dec 22];16(7):646–53. Available from: https://onlinelibrary.wiley.com/doi/10.1111/j.1365-2850.2009.01429.x

100. Jones K, Perlman CM, Hirdes JP, Scott T. Screening cognitive performance with the resident assessment instrument for mental health cognitive performance scale. Can J Psychiatry [Internet]. 2010 Nov 1 [cited 2021 Nov 29];55(11):736–40. Available from: http://journals.sagepub.com/doi/10.1177/070674371005501108

101. Hirdes JP, Ljunggren G, Morris JN, Frijters DH, Finne Soveri H, Gray L, et al. Reliability of the interRAI suite of assessment instruments: A 12-country study of an integrated health information system. BMC Health Serv Res [Internet]. 2008 Dec 30 [cited 2020 Nov 21];8(1):1–11. Available from: https://link.springer.com/articles/10.1186/1472-6963-8-277

102. Ontario Mental Health Reporting System — Data Quality Documentation, 2019–2020. Ottawa, ON; 2020.

103. Victorson D, McMahon M, Horowitz B, Glickson S, Parker B, Mendoza-Temple L. Exploring cancer survivors' attitudes, perceptions, and concerns about using medical cannabis for symptom and side effect management: A qualitative focus group study. Complement Ther Med. 2019 Dec 1;47:102204.

104. McTaggart-Cowan H, Bentley C, Raymakers A, Metcalfe R, Hawley P, Peacock S. Understanding cancer survivors' reasons to medicate with cannabis: A qualitative study based on the theory of planned behavior. Cancer Med [Internet]. 2021 Jan 17 [cited 2022 Jan 5];10(1):396–404. Available from: https://onlinelibrary.wiley.com/doi/10.1002/cam4.3536

105. Minerbi A, Häuser W, Fitzcharles M-A. Medical Cannabis for Older Patients. Drugs Aging [Internet]. 2018 [cited 2022 Jan 5]; Available from: https://doi.org/10.1007/s40266-018-0616-5

106. McHugh RK, Votaw VR, Sugarman DE, Greenfield SF. Sex and gender differences in substance use disorders [Internet]. Vol. 66, Clinical Psychology Review. Elsevier Inc.; 2018 [cited 2022 Jan 24]. p. 12–23. Available from: /pmc/articles/PMC5945349/

107. Greaves L, Hemsing N. Sex and Gender Interactions on the Use and Impact of Recreational Cannabis. Int J Environ Res Public Health [Internet]. 2020 Jan 14 [cited 2022 Jan 24];17(2):509.

Available from: https://www.mdpi.com/1660-4601/17/2/509

108. Schoeler T, Monk A, Sami MB, Klamerus E, Foglia E, Brown R, et al. Continued versus discontinued cannabis use in patients with psychosis: A systematic review and meta-analysis. The Lancet Psychiatry [Internet]. 2016 Mar 1 [cited 2020 Dec 29];3(3):215–25. Available from: http://dx.doi.org/10.1016/

109. Jongsma HE, Gayer-Anderson C, Lasalvia A, Quattrone D, Mulè A, Szöke A, et al. Treated incidence of psychotic disorders in the multinational EU-GEI study. JAMA Psychiatry [Internet]. 2018 Jan 1 [cited 2021 Nov 29];75(1):36–46. Available from: https://jamanetwork.com/

110. Jongsma HE, Turner C, Kirkbride JB, Jones PB. International incidence of psychotic disorders, 2002–17: a systematic review and meta-analysis. Lancet Public Heal [Internet]. 2019 May 1 [cited 2021 Nov 29];4(5):e229–44. Available from: /pmc/articles/PMC6693560/

111. Ajnakina O, Lally J, Di Forti M, Stilo SA, Kolliakou A, Gardner-Sood P, et al. Utilising symptom dimensions with diagnostic categories improves prediction of time to first remission in first-episode psychosis. Schizophr Res. 2018 Mar 1;193:391–8.

112. Ravichandran C, Cohen BM. Clinical Features of Psychotic Disorders: Comparing Categorical and Dimensional Models. Psych Res Clin Pr. 2021;3:29–37.

113. Cannabis Legalization and Regulation [Internet]. [cited 2022 Jan 20]. Available from: https://www.justice.gc.ca/eng/cj-jp/cannabis/

114. Gaskell GD, Wright DB, O'muircheartaigh CA. Telescoping of landmark events: implications for survey research . Vol. 64, Public Opinion Quarterly.

115. Rodriguez V, Alameda L, Trotta G, Spinazzola E, Marino P, Matheson SL, et al. Environmental Risk Factors in Bipolar Disorder and Psychotic Depression: A Systematic Review and Meta-Analysis of Prospective Studies. Schizophr Bull [Internet]. 2021 Jul 8 [cited 2021 Nov 29];47(4):959–74. Available from: https://academic.oup.com/schizophreniabulletin/article/47/4/959/6105805

116. Rutherford L, Stark A, Ablona A, Klassen BJ, Higgins R, Jacobsen H, et al. Health and well-being of trans and non-binary participants in a community-based survey of gay, bisexual, and queer men, and non-binary and Two-Spirit people across Canada. Rendina HJ, editor. PLoS One [Internet]. 2021 Feb 11 [cited 2021 Nov 29];16(2):e0246525. Available from: https://dx.plos.org/10.1371/journal.pone.0246525

117. Cannabis health warning messages - Canada.ca [Internet]. [cited 2021 Nov 29]. Available from:

https://www.canada.ca/en/health-canada/services/drugs-medication/cannabis/laws-regulations/regulations-support-cannabis-act/health-warning-messages.html

118. Smith J, Smith J, Mader J, Guestier G, Conn L, Maddigan J. An Exploration of Self-Reported Medicinal Cannabis Use Among a Sample of Eastern Canadian Postsecondary Students. J Behav Heal Serv Res [Internet]. 2021 Jul 8 [cited 2021 Nov 29];1–13. Available from: https://link.springer.com/article/10.1007/s11414-021-09763-3

119. Wadsworth E, Leos-Toro C, Hammond D. Mental Health and Medical Cannabis Use among Youth and Young Adults in Canada. Subst Use Misuse [Internet]. 2020 Feb 17 [cited 2021 Nov 29];55(4):582–9. Available from: https://www.tandfonline.com/doi/abs/10.1080/10826084.2019.1691594

120. Leos-Toro C, Shiplo S, Hammond D. Perceived support for medical cannabis use among approved medical cannabis users in Canada. Drug Alcohol Rev [Internet]. 2018 Jul 1 [cited 2021 Nov 29];37(5):627–36. Available from: https://onlinelibrary.wiley.com/doi/10.1111/dar.12823

121. Jenkins EK, Slemon A, Haines-Saah RJ. Developing harm reduction in the context of youth substance use: Insights from a multi-site qualitative analysis of young people's harm minimization strategies. Harm Reduct J [Internet]. 2017 Jul 31 [cited 2021 Nov 29];14(1):53. Available from: http://harmreductionjournal.biomedcentral.com/articles/10.1186/s12954-017-0180-z