Introduction

A large and growing body of evidence shows there is an association between cannabis use and psychotic disorders. Cannabis use disorders are highly prevalent in people with a diagnosis of schizophrenia, with a recent review showing up to 28.6% of people with schizophrenia have a current cannabis use disorder. This is considerably higher than the prevalence of cannabis use disorders in the general population, which is 1.5% to 2.2%. Moreover, studies suggest that cannabis use increases the risk of psychosis-related outcomes later in life.

Psychotic disorders, such as schizophrenia, are characterised by five types of symptoms: delusions (fixed beliefs that do not change in light of conflicting evidence), hallucinations (sensory perceptions in the absence of sensory stimulation), disorganised speech, disorganised or catatonic behaviour, and negative symptoms (i.e., reduced emotional expression or avolition). Though similar symptoms may occur transiently in the general population and need not indicate psychopathology, psychotic disorders are distinguished by the frequency and persistence by which psychotic symptoms occur. For instance, for a diagnosis of schizophrenia to be made, a person needs to have experienced at least two of the above symptoms (and at least one symptom being delusions, hallucinations, or disorganised speech) for a significant portion of the time over a one month period, which persist (to any extent) for a minimum of six-months (assuming that symptoms are not attributable to the direct physiological effects of a drug or another medical condition and that there is an absence of significant mood symptoms).

Though the association between cannabis use and psychotic disorders is well-supported by existing research, the exact nature of the association remains subject to debate. This bulletin reviews the epidemiological and clinical investigations into the relationship between cannabis use and psychosis as well as summarises research in related areas such as bipolar disorder and cannabis-induced psychosis.

Cannabis use as a risk factor for psychosis and psychosis-related outcomes

Prospective cohort studies suggest that cannabis use may increase the risk of psychosis-related outcomes. Though such findings are often cited as demonstrating a causal role for cannabis use in the development of psychotic disorders, whether or not this is actually the case remains a matter of debate. As suggested by researchers in the area (e.g., 9), evidence of an association between cannabis and psychosis should be considered against a set of criteria for causal inferences (i.e., the Bradford Hill criteria for causal inferences). The more of the following criteria that are met, the more likely it is that an association is causal:
1. Strength of association – A strong association between a risk factor and outcome is more likely to be causal than a weak association.

Numerous longitudinal studies have shown that cannabis use is associated with a significant risk of psychotic symptoms and/or disorders. In a 27-year follow-up study of around 50,000 Swedish conscripts, participants who used cannabis heavily by the age of 18 were found to be three times more likely to be diagnosed with schizophrenia at follow-up after controlling for well-known confounders such as living in a city, other drug use, and psychiatric diagnosis at age 18. Relatively more studies have found a significant effect of cannabis use on psychotic symptoms, as opposed to psychotic disorders. For instance, in a longitudinal cohort study, adolescents who had used cannabis by age 15 were found to be six times more likely to experience psychotic symptoms at age 26 than adolescents who had not (after controlling for psychotic symptoms at age 11). Across studies, cannabis use has been shown to increase the risk of psychosis-related outcomes (disorder or symptoms) by about 1.5 times. Though this might not be considered a strong effect, it is a robust one that persists while controlling for various important confounders.

2. Consistency – An association is more likely to be causal if it is found repeatedly across different studies using different methods and populations.

The finding that cannabis use increases the risk of psychosis symptoms has now been repeated by multiple studies using different populations and various study methods. For example, cannabis use was found to double the risk of psychotic symptoms one year later in a sample of 2295 participants, aged 18 to 49 years, who had not experienced any symptom of psychosis at baseline. In another study, cannabis use was found to increase the risk of psychotic symptoms four years later among a sample of 2437 young people aged 14 to 24 years. Findings of cannabis use increasing the risk of psychotic disorders, however, are less consistent. While the previously mentioned study of Swedish conscripts found an association between heavy cannabis use before age 18 and diagnosis of schizophrenia 27 years later, other studies have failed to find a similar effect of cannabis use on psychotic disorders (e.g., 11). However, as argued by the authors of the latter studies, this is likely due to reduced power owing to small sample sizes, a limitation inherent to studying low prevalence disorders, such as psychotic disorders.

3. Temporality – For a risk factor to be causally related to an outcome it needs to have preceded the outcome.

To be able to argue that cannabis use carries an increased risk of psychosis, studies need to show that cannabis use preceded the onset of psychotic symptoms and not vice versa. Strong support for temporality comes from prospective studies where the baseline sample has never used cannabis nor experienced any psychotic symptoms. One such study followed participants over a ten year period and assessed cannabis use and psychotic symptoms at baseline (to exclude participants who had ever used cannabis or had ever experienced any symptoms of psychosis), at 3.5 years follow-up (T2), and again at about eight years follow-up (T3). This study found that incident cannabis use between baseline and T2 increased the risk of experiencing incident psychotic symptoms between T2 and T3. Importantly, this study also found that psychotic symptoms at T2 did not predict incident cannabis use between T2 and T3, thus ruling out reverse causality.
4. Biological gradient – The association between a risk factor and outcome is more likely to be causal if there is evidence of a dose-response effect, that is, the greater the exposure to the risk factor, the greater the effect on the relevant outcome.

Several studies have found that the association between cannabis use and psychosis-related outcomes is dose dependent; that is, the effect that cannabis use has on psychosis risk is greater with higher levels of use\(^\text{12,16}\). For instance, in a three year longitudinal study of 4045 asymptomatic participants aged 14 to 80, not only did any cannabis use at baseline predict the presence of symptoms of psychosis three years later but more frequent use carried significantly greater risk of experiencing symptoms at follow-up than less frequent use\(^\text{16}\). A similar dose effect was found in a four year longitudinal study in a sample of 2437 participants aged 14 to 24 years: controlling for psychosis symptoms at baseline, more frequent cannabis use at baseline was associated with a higher risk of experiencing psychosis symptoms four years later than less frequent use\(^\text{12}\).

5. Coherence – The association is more likely to be causal if the causal interpretation of the association between risk factor and outcome is in line with existing evidence.

The criterion of coherence has been more difficult to establish for the relationship between cannabis use and psychosis. An example that would meet this criterion would be finding an increased incidence of psychotic disorders in the context of an increased prevalence of cannabis use. However, across a 30 year period in Australia, an apparent rise in the prevalence of cannabis use was not found to be coupled with an increased incidence of schizophrenia\(^\text{17}\). As discussed by the authors of this study, coherence of evidence is difficult to obtain in the context of all other factors present (other than the association between cannabis use and psychosis), including concurrent changes in many well-known environmental risk factors for psychosis such as improved maternal nutrition and antenatal care. Given that cannabis use may be but one of many known risk factors for psychosis-related outcomes, non-coherence of evidence is not necessarily inconsistent with a causal account.

6. Specificity – An association between a risk factor and an outcome is more likely to be causal if it is specific to the outcome in question (as opposed to various outcomes).

For this criterion to be met, the evidence should show that cannabis use is a risk factor for psychosis-related outcomes specifically (as opposed to a wide range of health-related outcomes). A recent review\(^\text{1}\) that shows cannabis use to increase risk of only psychosis-related outcomes and less so affective mental-health outcomes (e.g., major depression and anxiety disorders) may be considered as evidence of specificity. A growing body of evidence revealing a role for cannabis use in bipolar disorder\(^\text{18}\), in addition to evidence of shared genetics in bipolar disorder and psychotic disorders\(^\text{19}\), adds further support for the criteria of specificity.

7. Plausibility – An association is more likely to be causal if the causal interpretation is biologically plausible.

This criterion requires that a causal interpretation of the association between cannabis use and psychosis is based upon plausible biological mechanisms. A proposed biological mechanism involves a cannabis-induced sensitisation of dopaminergic activity for which genetically predisposed individuals may be more vulnerable\(^\text{20,21}\). The role of dopamine transmission in psychosis has been long documented through findings such as the effectiveness of dopamine-receptor blockers in reducing symptoms of psychosis\(^\text{22}\) and the ability of amphetamines, which
enhance dopaminergic transmission, to induce positive symptoms of psychosis. According to this view, cannabis use may interact with genetic predisposition and other environmental factors (such as early life stress) to progressively sensitize THC-mediated dopaminergic transmission. This effect appears to be neuro-developmentally mediated such that early adolescent use carries a particularly high risk for predisposed individuals.

8. Experimental evidence – There is evidence from experimental study designs and/or animal studies that is in line with the causal explanation.

There are several lines of experimental evidence, both animal and human, that support a causal association between cannabis use and psychosis. One such line of evidence comes from studies using animal models of schizophrenia, such as reduced prepulse inhibition (PPI). PPI refers to the reduction in startle to a loud pulse, when it is followed shortly before by a softer pulse. People with schizophrenia typically show reduced PPI compared to people without schizophrenia. Animal research has pointed to PPI being sensitive to cannabis-related changes in neurodevelopmental processes: rats chronically exposed to cannabinoids in puberty show deficits in PPI when tested later in adulthood, whereas rats exposed to cannabinoids following puberty do not. Assuming reduced PPI in rats is a valid animal model for sensorimotor gating deficits in schizophrenia, such evidence could be seen to support, at least in part, the view that cannabis use in early adolescence plays a causal role in the development of psychosis-related outcomes in adulthood.

Experimental and quasi-experimental studies in humans also support a causal link between cannabinoid exposure and psychosis. For instance, in double-blind within-subject studies, healthy adults show greater psychosis-like symptoms, positive and negative, in response to intravenous THC compared with placebo. Further, in line with the above explanation of cannabis-induced sensitisation of dopaminergic activity in predisposed individuals, THC exposure has been found to selectively increase dopaminergic activity in first-degree relatives of patients with a psychotic disorder and people with a psychotic disorder (compared to healthy individuals). In combination, these animal and human studies show that cannabis use can induce psychosis-like symptoms and that predisposed individuals and adolescents may be particularly sensitive to its effects on brain activity and/or neurodevelopment.

9. Analogy – The association between the risk factor and outcome is similar to that between another risk factor and outcome in which causality has been established.

An analogy for the role that cannabis use plays in the development of psychosis would be similar to another health condition for which many risk factors contribute to its development. It is, however, very difficult to establish causality between a risk factor and outcome when many risk factors are involved and, as such, the analogies available are limited. A possible analogy might be a high sodium diet as a risk factor for hypertension; a high sodium diet carries a risk of hypertension and does so to a greater extent in vulnerable individuals (a high sodium diet is associated with greater increases in blood pressure in people who are overweight). Genes also influence one's sensitivity to blood pressure changes following increased salt intake, as well as hypertension in general. Thus, a young person predisposed to psychosis who uses cannabis at 15 years of age would have an increased risk of developing psychosis compared with an adult who uses cannabis for the first time in adulthood and who is not predisposed. Likewise, an overweight person who is genetically predisposed to higher salt sensitivity and/or hypertension in general will be at a greater risk of experiencing high blood pressure compared to someone who does not have a genetic predisposition nor is overweight.
Cannabis use in individuals predisposed to psychosis

For individuals predisposed to psychosis, cannabis use has been found to carry a higher risk of later psychosis-related outcomes, compared to non-predisposed individuals (e.g.,11, 12, 16, 25). Specifically, cannabis use carries a greater risk of increasing psychotic symptoms in those who are already experiencing a range of subclinical symptoms of psychosis11, 12, 16 as well as for those who carry specific genotypes linked to psychosis, e.g., the COMT valine/valine (val/val) genotype25. For instance, a recent study found that participants who carried the COMT val/val genotype and who used cannabis before the age of 17 were over ten times more likely to develop schizophreniform disorder (when symptoms of psychosis are present for at least one month but less than six months) than those who carried the same genetic phenotype but who did not use cannabis before that age. In contrast, those who carried the COMT met/met genotype were not found to carry a higher risk of psychotic disorder depending on cannabis use25. A recent study suggests further that there may be shared genetic variance between schizophrenia and cannabis use such that people with a genetic predisposition to schizophrenia may be more likely to use cannabis and use it at greater quantities32.

Cannabis use by people with an established psychotic disorder

A connected line of research looks at the effects of cannabis use in people with schizophrenia and other psychoses. Cannabis use is associated with a younger age of onset of psychotic illness33. Cannabis use in first-episode psychosis (FEP) is associated with poorer medication compliance3. Further, a recent study34 has shown that, after controlling for insufficient antipsychotic treatment and baseline symptoms, patients who continued using cannabis after FEP had greater psychotic symptoms and poorer social functioning at follow-up, five years later, than patients who did not use cannabis or who had stopped using it after FEP. Thus, continued cannabis use following the onset of psychosis negatively impacts treatment outcomes over and above the negative impact had by cannabis use on medication non-compliance. Ceasing use following FEP can reduce the negative impact of cannabis use on treatment outcomes34.

Cannabis use and bipolar disorder

A similar pattern of evidence has been found for an association between cannabis use and bipolar disorder. Specifically, cannabis use disorders are more prevalent among people with bipolar disorder than those without and are associated with a more severe course of bipolar illness35. Regarding the directionality of the association, a recent prospective study has shown that cannabis use increases the risk of subsequent manic symptoms after controlling for a wide range of confounding factors, as well as baseline depressive and manic symptoms. Importantly, this finding was independent of psychotic symptoms at baseline and at follow-up18. Further, research has shown that cannabis use is associated with a younger onset of bipolar disorder and that this effect may be dose-dependent36. Despite the similarities in research findings between the role of cannabis use in psychotic disorders and in bipolar disorder, supporting evidence for the latter is less well-established. It would not be surprising if future research confirms similar roles for cannabis use considering the genetic overlap between psychotic disorders, such as schizophrenia, and bipolar disorder19.

Is there a distinct cannabis-induced psychosis?

There are a considerable number of reports of people experiencing a psychotic episode following heavy cannabis use. This has led to some researchers and clinicians arguing for the existence of a cannabis-induced psychosis, also known as toxic psychosis. As described in the literature37, cannabis-induced psychosis is characterised by the following features: a short onset after cannabis use; a duration of at least one day; occurs in individuals without a history of psychiatric disorder.
prior to cannabis use; undergoes remission following cessation of use; and reemerges if cannabis use is resumed. Unfortunately, the majority of past research in this area has suffered various methodological problems (e.g. poor diagnostic criteria, small sample size) and this has commonly been used to argue against cannabis-induced psychosis being a separate diagnostic entity (see 37 for a review). Improved recent studies comparing cannabis-induced psychosis with acute schizophrenia have found some differences in terms of premorbid patient characteristics and presenting symptoms38. A recent review39 has suggested that cannabis-induced psychosis presents with more positive and less negative symptoms than psychosis not related to cannabis use but argued that the evidence to date was insufficient to support cannabis-induced psychosis as a qualitatively distinct diagnostic entity. Given the above mentioned research showing increased dopaminergic transmission in response to THC in patients with psychosis and unaffected first-degree relatives20 and the ability of dopaminergic agents to induce positive symptoms of psychosis23, it may be argued that such THC-mediated dopaminergic activity (and one's predisposition to it) may underlie cannabis-induced psychosis. This suggestion implies that cannabis-induced psychosis involves a predisposition to psychotic disorders. This would be in line with recent evidence that individuals with cannabis-induced psychosis have a particularly high conversion rate to schizophrenia, over and above that seen in other substance-induced psychoses. Importantly, this finding highlights the need for researchers and clinicians to direct greater attention towards cannabis-induced psychosis as a clinically significant entity in its own right40.

Summary

In summary, research suggests that cannabis use is associated with an increased risk of psychotic symptoms and disorders. This risk is greater for young people11, 25, 41 and predisposed individuals, such as those who are already experiencing subclinical symptoms of psychosis22 or who carry a genetic predisposition22. Continued use of cannabis following the onset of psychotic illness negatively impacts medication compliance, symptom severity, and social outcomes. Cannabis use may also increase risk for other disorders, such as bipolar disorder, but the evidence to date is very limited. Another area where research is limited is that of cannabis-induced psychosis. Given recent research showing a high conversion rate from cannabis-induced psychosis to schizophrenia, future research should be directed towards better understanding its aetiology and treatment.
References


