

Review

Cannabis and psychosis: Have we found the missing links?



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ABSTRACT

Background: The association between cannabis and psychosis has long been a matter of debate, with cannabis widely perceived as a harmless recreational drug.

Methods: Electronic bibliographic databases like PubMed and Google Scholar were searched using the format “(psychosis or schizophrenia or synonyms) and (cannabis or synonyms)”. Cross-linked searches were made taking the lead from key articles. Recent articles and those exploring the genetic factors or gene–environment interaction between cannabis use and psychosis were focussed upon.

Results: Heavy cannabis use at a young age, in association with genetic liability to psychosis and exposure to environmental stressors like childhood trauma and urban upbringing increases the risk of psychotic outcome in later life.

Conclusion: Cannabis acts as a component cause of psychosis, that is, it increases the risk of psychosis in people with certain genetic or environmental vulnerabilities, though by itself, it is neither a sufficient nor a necessary cause of psychosis. Although significant progress has been made over the last few years, we are yet to find all the missing links. Further work is necessary to identify all the factors that underlie individual vulnerability to cannabis-related psychosis and to elucidate the biological mechanisms underlying this risk.

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1. Introduction

The psychotropic properties of cannabis have been known since time immemorial, but whether cannabis has detrimental effects on health has been a matter of debate. In 1893, Indian Hemp Commission established by the British government concluded in its seven-volume report that there was no evidence of any weight regarding mental and moral injuries from moderate use of cannabis (Kaplan, 1969). Even after the passage of a century, it continued to be widely accepted in the medical fraternity that smoking cannabis did not cause long-term harm to health and cannabis came to be perceived as a drug of recreational use like alcohol and tobacco. However, over the last decade or so, there has been a spate of evidence on the mental health risks of long-term use of cannabis and a number of studies have furthered our understanding of the effects of cannabis on the brain, though it remains to be seen if all the missing links are in place.

There is ample evidence from case reports and surveys of cannabis users in the general population that cannabis can produce acute psychotic symptoms which are transient and recover completely on abstinence (Chopra and Smith, 1974; Keeler et al., 1971; Talbott and Teague, 1969; Thomas, 1996). In relation to this, some researchers proposed that “cannabis-induced psychosis” be considered a distinct diagnostic entity (Mathers and Ghodse, 1992; Rottanburg et al., 1982; Thakore and Shukla, 1976). However, others argued that cannabis-induced psychosis is not clinically different from other psychotic disorders and could be an early sign of schizophrenia rather than a distinct clinical entity (Arendt et al., 2005; McGuire et al., 1994). In further support of this, a population-based cohort study found no difference in familial predisposition to psychotic disorders between patients with cannabis-induced psychosis and those with schizophrenia (Arendt et al., 2008).

2. Is there an association between cannabis and schizophrenia?

It is well known that regular cannabis use and psychotic disorders such as schizophrenia are associated in the general population (Degenhardt and Hall, 2001; Tien and Anthony, 1990) and heavy cannabis users are over-represented among new cases of schizophrenia (Barbee et al., 1989). However, the strongest evidence that cannabis use may have a causal association with schizophrenia comes from longitudinal studies of large representative samples of the population who have been followed up to see if cannabis users are at higher risk of developing schizophrenia. The earliest such evidence came from a 15-year prospective study of cannabis use and schizophrenia by Andreasson et al. (1987) who examined around 50,000 Swedish conscripts. They found that those who had tried cannabis by age 18 were 2.4 times more likely to be diagnosed with schizophrenia 15 years later than those who had not and the risk of this diagnosis increased to around six times with higher frequency of cannabis use. The risks were substantially reduced but still significant after statistical adjustment for variables that were related to the risk of developing schizophrenia.

The 27-year follow-up of the Swedish cohort by Zammit et al. (2002) also found a dose–response relationship between frequency of cannabis use at baseline and risk of schizophrenia during the follow-up. Again, the relationship between cannabis use and schizophrenia persisted even after statistically controlling for the effects of other substance use and other potential confounding factors, including a history of psychiatric symptoms at baseline. Assuming a causal relationship, and given current patterns of use, the authors estimated that 13% of cases of schizophrenia could be averted if all cannabis use was prevented. The recently published 35-year follow-up of the same cohort also supported these results (Manrique-Garcia et al., 2012). As shown in Table 1, these findings have been supported by other prospective cohort studies from the Netherlands, New Zealand, Germany and elsewhere (Arseneault et al., 2002; Fergusson et al., 2003; Henquet et al., 2005; van Os et al., 2002).

Moore et al. (2007) published a meta-analysis of seven longitudinal studies on the relationship between cannabis and psychosis and reported an increased risk (odds ratio = 1.4) of any psychotic outcome in individuals who had ever used cannabis. Findings were consistent with a dose–response effect, with greater risk in people who used cannabis more frequently. The studies included in the meta-analysis adjusted for about 60 confounding factors, including other substance use, personality traits, socio-demographic markers, intellectual ability, other mental health problems etc. In order to address concerns about unmeasured confounding variables, McGrath et al. (2010) conducted a sibling pair analysis nested within a prospective birth cohort and found that early cannabis use is associated with psychosis-related outcomes in young adults.

A recent meta-analysis found that the age at onset of psychosis for cannabis users was 2.70 years younger than for nonusers while alcohol use was not associated with a significantly earlier age at onset of psychosis (Large et al., 2011). In a study of heavy cannabis users who went on to develop psychosis, Galvez-Buccollini et al. (2012) found that age at onset of cannabis use was directly associated with age at onset of psychosis and age at first hospitalization. That the association remained significant even after adjusting for potential confounding factors is, according to the authors, consistent with the hypothesis that cannabis can cause or precipitate the onset of psychosis after a prolonged period of time.

3. Can the association be explained by reverse causality?

A possible explanation of the association is that cannabis use is a consequence, rather than a cause, of schizophrenia. Cannabis is known to improve negative and depressive symptoms and may be used to self-medicate symptoms of schizophrenia (Schneier and Siris, 1987). In order to counter this, some longitudinal studies excluded patients with psychotic symptoms at baseline or made statistical adjustments for the same and yet found an increased risk of psychosis in cannabis users (Arseneault et al., 2002; van Os et al., 2002). Moreover, a recent study reported that age at initiation of cannabis use predicts the age at onset of psychosis, with the gap being approximately 7–8 years (Stefanis et al., 2013).

Table 1
General population studies of the effect of cannabis use on the risk of psychosis.

Authors	Sample	Follow-up	Odds ratio (95% confidence interval)
Andreasson et al. (1987)	45,570 Swedish male conscripts	15 years	6.0 (4.0–8.9)
Zammit et al. (2002)	50,087 Swedish male conscripts	27 years	3.1 (1.7–5.5)
Arseneault et al. (2002)	1037 New Zealander males and females from Dunedin birth cohort	15 years	3.1 (0.7–13.3)
van Os et al. (2002)	4104 Dutch males and females from population sample, aged 18–64 (NEMESIS)	3 years	2.8 (1.2–6.5)
Fergusson et al. (2003)	1265 New Zealander males and females from Christchurch birth cohort (CHDS)	3 years	1.8 (1.2–2.6)
Henquet et al. (2005)	2437 German males and females from population sample, aged 14–24 (EDSP)	4 years	1.7 (1.1–2.5)
Manrique-Garcia et al. (2012)	50,087 Swedish male conscripts	35 years	3.7 (2.3–5.8)

4. Impact of cannabis on course of schizophrenia

Negrete et al. (1986) conducted a retrospective study of the relationship between self-reported cannabis use and schizophrenia and found higher rates of positive symptoms, and more hospitalizations among active cannabis users. These relationships persisted after statistical adjustment for age and sex differences between the user groups. In a prospective study over one year of follow-up, Linszen et al. (1994) found that cannabis users relapsed to psychotic symptoms sooner, and had more frequent relapses than non-users. There was also a dose–response relationship, with the daily users relapsing earlier and more often than the less than daily users who, in turn, relapsed sooner, and more often, than non-users. These relationships persisted after multivariate adjustment for premorbid adjustment, and alcohol and other drug use during the follow-up period. In a ten year follow-up study, Foti et al. (2010) reported that the relationship between cannabis use and the course of illness in schizophrenia is bidirectional. They concluded that cannabis use is associated with an adverse course of psychotic symptoms in schizophrenia, and vice versa, even after taking into account other clinical, substance use, and demographic variables. In another study, it was found that stopping cannabis use after the first psychotic episode was associated with a clear improvement in outcome (Gonzalez-Pinto et al., 2009).

Thus, there is strong evidence from prospective observational cohort studies in favour of the view that cannabis increases the risk of psychotic outcome independent of confounders, and also worsens the course and outcome of pre-existing psychotic disorders. However, the question that follows is whether a causal association is biologically plausible or not and why only a small proportion of cannabis users go on to develop psychosis.

5. Is the association biologically plausible?

Although the epidemiological link between cannabis and psychosis has been investigated extensively, the biological basis of this association remains poorly understood. There is ample indirect evidence for the biological basis in the form of the presence of alterations in the endocannabinoid system in schizophrenia. Studies on schizophrenic patients have shown up-regulation of cannabinoid-1 (CB1) receptors in cortical brain regions such as the dorsolateral prefrontal cortex (Dalton et al., 2011; Dean et al., 2001) and in cingulate cortex (Newell et al., 2006; Wong et al., 2010; Zavitsanou et al., 2004). However, some studies have yielded contrasting results. No change was found in the anterior cingulate cortex by Koethe et al. (2007) while Eggen et al. (2008) reported decrease in CB1 receptor expression in the prefrontal cortex. Antipsychotics have been reported to decrease prefrontal cortex CB1 receptor expression in schizophrenic patients (Urigen et al., 2009). Cannabinoid-2 (CB2) receptors have also been implicated in schizophrenia. Clinical remission of schizophrenia has been shown to be accompanied by a significant decrease in CB2 receptor mRNA levels in the blood (De Marchi et al., 2003). Ishiguro et al. (2010) reported an increased risk of schizophrenia for people with low CB2 receptor function. Anandamide levels are significantly elevated in schizophrenia patients, both in the cerebrospinal fluid and in the blood (De Marchi et al., 2003; Giuffrida et al., 2004; Koethe et al., 2009; Leweke et al., 1999). In addition, there is direct evidence of cannabis leading to structural, neuro-physiological and neuro-chemical changes in the brain which are similar to those seen in schizophrenia.

5.1. Cannabis and structural brain changes

Long-term heavy cannabis use may lead to reduced hippocampal and amygdala volumes (Yucel et al., 2008) and smaller

cerebellar white-matter volume similar to that observed in schizophrenia (Solowij et al., 2011). Cannabis exposure has also been shown to be associated with bilateral thalamic volume loss in currently unaffected people at familial high risk of developing schizophrenia (Welch et al., 2011). However, it seems unlikely that the structural brain changes can independently explain the increased risk of psychosis associated with use of cannabis (DeLisi, 2008).

5.2. Cannabis and dopaminergic hypothesis of schizophrenia

The dopaminergic hypothesis of schizophrenia postulates that positive symptoms of schizophrenia are due to increased dopaminergic activity in the mesolimbic tract while reduced dopaminergic activity in prefrontal cortex might be linked to negative and cognitive symptoms. Dopamine neuronal firing in the ventral tegmental area of midbrain is controlled by excitatory glutamatergic and inhibitory GABAergic inputs, which in turn are reciprocally modulated by endocannabinoids released from dopaminergic dendrites via retrograde signalling (Lupica and Riegel, 2005; Matyas et al., 2008; Melis et al., 2004). Exogenous cannabinoids disrupt the retrograde endocannabinoid signalling and result in excess dopaminergic transmission in the mesolimbic tract (Cheer et al., 2004; French et al., 1997; Riegel and Lupica, 2004), leading to positive symptoms. In addition to influencing dopaminergic neurotransmission in the mesolimbic pathway, cannabis also seems to affect dopaminergic neurotransmission in the prefrontal cortex. In particular, repeated exposure to cannabis has been found to decrease dopamine levels in the prefrontal cortex (Jentsch et al., 1998; Verrico et al., 2003).

It has been suggested that, in schizophrenia, dopamine dysregulation results in a psychological state of aberrant salience, in which mundane events and ideas may be attributed with undue significance, leading to positive symptoms (Kapur et al., 2005). A recent study by Bhattacharyya et al. (2012a) found that delta-9-tetrahydrocannabinol increases the aberrant attribution of salience and thus, cannabis may induce psychotic symptoms by this mechanism.

5.3. Cannabis and neurodevelopmental hypothesis of schizophrenia

One view of schizophrenia is that it is a neurodevelopmental disorder (Rapoport et al., 2005; Weinberger, 1996). Endocannabinoids play an important role in several processes important in neurodevelopment, including neurogenesis, neural specification, neural maturation, neuronal migration, axonal elongation, and glia formation (D'Souza et al., 2009; Galve-Roperh et al., 2007). Exposure to exogenous cannabinoids in adolescence can lead to a disturbance of the endocannabinoid system in the brain and interfere with neurodevelopmental processes. This may provide a mechanism by which exposure to cannabinoids during adolescence may increase the risk for the development of schizophrenia.

5.4. Cannabis and electroencephalographic changes

Positive symptoms of schizophrenia have been linked to reduction in EEG coherence, which is a measure of the correlation of activity in different parts of the brain (Ford et al., 2002). Tetrahydrocannabinol has been shown to decrease theta coherence between the right and left frontal lobes and since the reduction in coherence was strongly associated with positive psychotic symptoms, this could be one of the mechanisms for the psychotogenic property of cannabis (Morrison et al., 2011).

6. Why is it that only a small proportion of cannabis users develop psychosis?

Although there is strong evidence that use of cannabis is associated with a higher risk of psychosis and also that the association is biologically plausible, the fact remains that the vast majority of cannabis users never go on to develop any psychotic symptoms. Some of the factors that influence the development of psychotic symptoms have been elucidated.

6.1. Amount and duration of cannabis use

Epidemiological studies investigating the association between cannabis use and development of psychotic symptoms have found a dose–response relationship indicating that long term heavy cannabis users are more likely to develop psychosis (Manrique-Garcia et al., 2012; Moore et al., 2007; van Os et al., 2002; Zammit et al., 2002).

6.2. Early exposure to cannabis

There is evidence to suggest that adolescence is a particularly vulnerable period for a person to be exposed to cannabis. A recent longitudinal cohort study found that cannabis use with onset prior to age of 14 years strongly predicted schizotypal symptoms in adulthood, independent of early adolescent schizotypal symptoms, major depression, anxiety disorder, other drug use, and cigarette use (Anglin et al., 2012). A birth cohort study from New Zealand found that the onset of cannabis use before the age of 15 years was associated with a greater risk of developing schizophreniform disorder at age 26 years than the onset of cannabis use at an older age (Arseneault et al., 2002). This finding has been replicated by other researchers as well (Konings et al., 2008; Stefanis et al., 2004).

A possible explanation is that cannabis interferes with the neuro-developmental processes in the brain by disrupting the endocannabinoid system which is important for neurogenesis (Galve-Roperh et al., 2007). Most parts of the brain undergo active remodelling in adolescence, before attaining maturation of function. It has been postulated that excessive activation of cannabinoid-1 receptors by cannabis use during adolescence reduces the level of glutamatergic drive needed for the functional maturation of prefrontal GABAergic interneurons, consequently impairing the development of mature brain functioning and resulting in increased liability for psychosis (Caballero and Tseng, 2012). In support of this hypothesis, it has been found that long term exposure to cannabis is associated with impaired axonal connectivity, with the damage being more severe in those who started regular cannabis use at an earlier age (Zalesky et al., 2012).

6.3. Differential sensitivity to delta-9-tetrahydrocannabinol

It is possible that some individuals are more sensitive to the psychotogenic effect of cannabis owing to certain genetic or environmental factors. In the absence of these factors, cannabis use may not result in psychosis. This can be one of the reasons why majority of cannabis users do not go on to develop psychosis.

6.3.1. Genetic factors

That one's genotype moderates his or her response to cannabis is an example of a gene–environment interaction. In a case–control study of patients with cannabis-associated psychosis, McGuire et al. (1995) found that the risk of schizophrenia was ten times higher for relatives of patients who developed psychosis using cannabis than for the relatives of patients who had not used cannabis and suggested that individuals who have a stronger

genetic liability for schizophrenia, indicated by the higher prevalence of schizophrenia in their family, are more vulnerable for the psychotogenic effect of cannabis.

A study by Caspi et al. (2005) on a functional polymorphism in the catechol-O-methyltransferase (COMT) gene was the first direct evidence of a gene–environment interaction in the cannabis–psychosis relationship. COMT is the enzyme that degrades dopamine, epinephrine, and norepinephrine. A functional polymorphism of the COMT gene results in two common allelic variants, the valine (Val), and the methionine (Met) allele, associated with high versus low enzyme activity, respectively. Caspi et al. (2005) reported that for individuals homozygous for the Val allele, the relative risk of developing psychotic illness after adolescent cannabis exposure was 10.9 while in individuals homozygous for the Met allele, the risk was only 1.1. However, a later study by Zammit et al. (2007) did not replicate this finding.

While many genes have been implicated, a sibling analysis and proband follow-up study conducted by van Winkel and the Genetic Risk and Outcome of Psychosis (GROUP) investigators (2011) examined interactions between cannabis use and 152 single-nucleotide polymorphisms in 42 candidate genes and found that variation in the AKT1 rs2494732 single nucleotide polymorphism may mediate both short-term as well as longer-term effects on psychosis expression associated with use of cannabis. AKT1 is a serine/threonine kinase that is involved in the phosphorylation of glycogen synthase kinase (GSK-3). It has been suggested that dopamine D2 receptors may signal through an AKT1/GSK-3 signalling pathway which is regulated by cannabinoids (Beaulieu et al., 2007). Since the cannabinoid-regulated AKT1/GSK modulation occurs downstream of the dopamine D2 receptor, van Winkel and the Genetic Risk and Outcome of Psychosis (GROUP) investigators (2011) postulated that this could potentially explain the poor response of substance-using patients with schizophrenia to antipsychotic treatment (Dixon, 1999). The findings were replicated in a recent case–control study by Di Forti et al. (2012) who concluded that genetic variation at rs2494732 of AKT1 gene influences the risk of developing a psychotic disorder in cannabis users.

However, it seems unlikely that variation in a single gene can explain the differential sensitivity to delta-9-tetrahydrocannabinol in individuals at risk for psychosis. It may be possible that more complex processes are involved wherein two or more genes may interact to cause psychosis in cannabis users or other environmental factors may interact with cannabis to cause psychosis in genetically vulnerable persons (Henquet et al., 2008). For example, presence of both COMT Val/Val genotype and liability to psychosis on psychometry has been shown to be associated with a greater likelihood of transient psychotic symptoms after cannabis (Henquet et al., 2006). Bhattacharyya et al. (2012b) recently reported that subjects with specific genotypes of both DAT1 and AKT1 were more sensitive to the psychotogenic effects of cannabis than subjects with only one of those, and that this effect involved an alteration in the neural response to delta-9-tetrahydrocannabinol in the dopamine-rich regions of striatum and midbrain, consistent with independent evidence that the psychotic effects of cannabis are mediated by dopamine.

6.3.2. Environmental factors

It has been found that presence of both childhood sexual trauma and cannabis use increases the risk of psychotic outcome (Houston et al., 2008, 2011). This was recently replicated in the analysis of prospective data from two independent population based studies from Greece and the Netherlands (Konings et al., 2012). Urban upbringing is another environmental factor that has been shown to increase vulnerability to the psychotogenic effects

of cannabis use later in life (Counnard et al., 2007; Kuepper et al., 2011). While the exact biological basis of this is not known, it has been proposed that repeated exposure to environmental stressors sensitizes one to the psychotogenic effects of delta-9-tetrahydrocannabinol (Henquet et al., 2008) and this cross-sensitization process is likely to be mediated by dopamine (Kuepper et al., 2010). Thus, both genetic and environmental factors can influence the progression from cannabis use to schizophrenia.

7. Does cannabis also have antipsychotic effects?

Delta-9-tetrahydrocannabinol and cannabidiol are the two major constituents found in cannabis, of which delta-9-tetrahydrocannabinol is the main psychoactive ingredient and is thought to be the ingredient responsible for the increased risk of developing schizophrenia following regular cannabis use. Cannabidiol, on the other hand, has been shown to have opposite effects to delta-9-tetrahydrocannabinol and may even have antipsychotic properties. A functional neuroimaging study reported that delta-9-tetrahydrocannabinol and cannabidiol had opposite effects on activation of brain regions and pretreatment with cannabidiol was able to prevent the acute induction of psychotic symptoms by delta-9-tetrahydrocannabinol (Bhattacharyya et al., 2010). Preliminary studies of cannabidiol in psychotic patients have shown positive therapeutic effects (Leweke et al., 2007; Zuardi et al., 1995, 2006, 2009). Reduced degradation of anandamide leading to enhanced anandamide signalling in the brain has been proposed as the mechanism for the antipsychotic effect of cannabidiol (Leweke et al., 2012). It remains to be seen if cannabidiol can be developed and marketed as an antipsychotic agent.

While cannabis potency varies widely between different places and different products, it is of concern that increasingly potent forms of cannabis with decreasing cannabidiol content are available on the street. Use of sinsemilla or skunk, which contains high levels of tetrahydrocannabinol and almost no cannabidiol, is gradually increasing and may lead to a spate in the incidence of psychosis (Henquet and Kuepper, 2010; Potter et al., 2008).

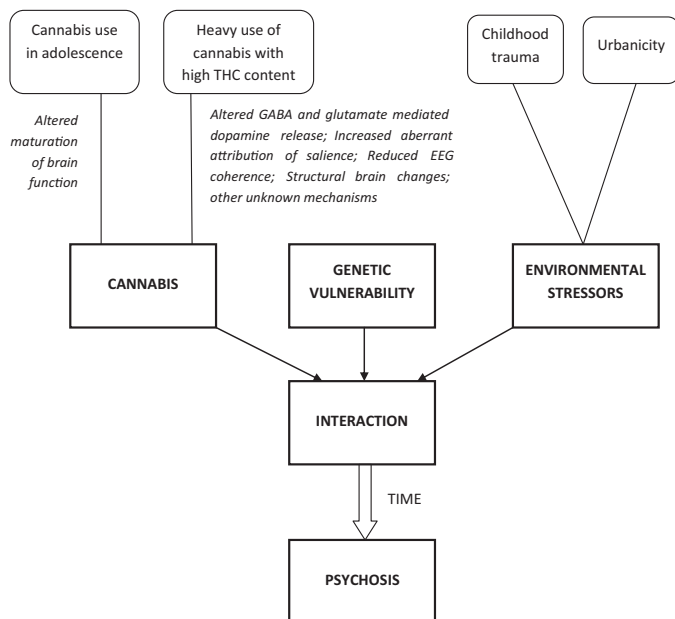


Fig. 1. Cannabis can cause psychosis only in the presence of other susceptibility factors which may be genetic or environmental, thus acting as a component cause. THC: Tetrahydrocannabinol, GABA: Gamma amino butyric acid, EEG: Electroencephalography

8. Cannabis as a component cause of psychosis

Heavy cannabis use, especially in the adolescence, is likely to increase the risk of psychotic disorder in later life, but by itself it is neither a necessary nor a sufficient cause. That is why, many cannabis users never go on to develop psychosis. It is only some people who have a high genetic liability to psychosis and may also have exposure to environmental stressors like childhood trauma and urban upbringing, who are highly vulnerable to the psychotogenic effects of cannabis, especially after heavy cannabis use in young age. Thus cannabis leads to psychosis only in the presence of other factors in the various causal pathways, thereby acting as a component cause of psychosis (Fig. 1). While some of these factors which interact with cannabis have been described, there may be others that are still unknown.

9. Conclusion

It is now known beyond doubt that cannabis acts as a component cause of psychosis, that is, it increases the risk of psychosis in people with certain genetic or environmental vulnerabilities, though by itself, it is neither a sufficient nor a necessary cause of psychosis. Genetic vulnerability, exposure to cannabis in adolescence, frequent heavy use of cannabis and use of potent forms of cannabis containing higher levels of tetrahydrocannabinol and lower levels of cannabidiol are the important factors that favour a progression to psychosis. Although significant progress has been made over the last few years and we now have a broad understanding of the biological pathway linking cannabis and psychosis, we are yet to find all the missing links and further research is needed before the exact mechanism of the same can be unravelled. Once all the missing links are in place and we have a precise knowledge of how cannabis leads to psychosis, it is hoped that newer and more efficacious antipsychotic agents, especially those that can reverse the detrimental effects of cannabis, can be developed. Till then, there is enough reason and sufficient evidence to warn young people that using cannabis could increase their risk of developing a psychotic illness later in life and warrant public health interventions like education campaigns to alert people to the possible risks associated with cannabis.

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Conflicts of interest

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