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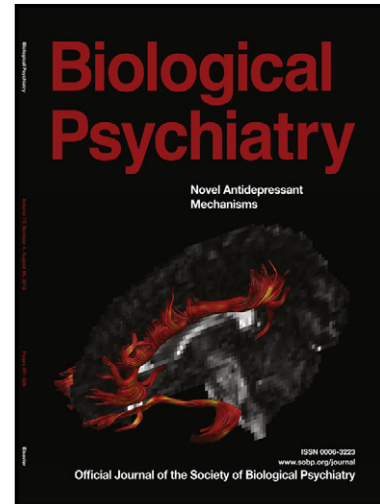
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Biological Psychiatry review**Association between cannabis and psychosis: epidemiological evidence**

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Abstract

Associations between cannabis use and psychotic outcomes are consistently reported, but establishing causality from observational designs can be problematic. We review the evidence from longitudinal studies that have examined this relationship and discuss the epidemiological evidence for and against interpreting the findings as causal. We also review the evidence identifying groups at particularly high risk of developing psychosis from using cannabis.

Overall, evidence from epidemiological studies provide strong enough evidence to warrant a public health message that cannabis use can increase the risk of psychotic disorders.

However, further studies are required to determine the magnitude of this effect, the effect of different strains of cannabis on risk, and to identify high-risk groups particularly susceptible to the effects of cannabis on psychosis. We also discuss complementary epidemiological methods that can help address these questions.

Introduction

Population studies consistently show that cannabis use is associated with psychotic experiences and disorders, including schizophrenia, but whether associations are causal is difficult to ascertain from observational designs. Randomised controlled trials in laboratory conditions provide evidence that delta-9-tetrahydrocannabinol (THC), the main active compound in cannabis, can induce transient psychotic-like experiences (1). However, these experiences resolve within a few hours and rarely cause distress, in contrast to psychotic disorder where experiences are prolonged and impairment often substantial.

It is important to establish whether the association between cannabis and psychotic disorder is causal, and to accurately estimate the magnitude of this effect, as cannabis might represent the most potentially modifiable risk factor for psychosis. Non-causal explanations for associations arising from observational studies include reverse causation (where associations reflect psychosis increasing risk of using cannabis), bias (where problems with measurement or sample selection lead to incorrect estimates), and confounding (where other variables that increase risk of both cannabis use and psychosis lead to spurious associations), and are discussed further below.

RCTs of cannabinoid use or interventions to reduce cannabis use tend to have follow-up periods too short to yield useful information about psychosis risk arising from long term use (2) and are not discussed further here. Nor do we review case-studies or studies relying on a diagnosis of cannabis-induced psychotic disorder, as such diagnoses are dependent on assumptions of a causal role of cannabis in specific cases by a clinician, and there is no robust evidence as far as we are aware of clinical characteristics that allow the distinction of this disorder to be made (3).

Evidence from case control and cross sectional studies

Evidence from most case-control and cross-sectional studies support an association between cannabis use and schizophrenia (4-6) and psychotic symptoms (7-9). A potential problem of case-control studies is selection bias arising from inadequate sampling of a control group, and in both these designs reverse causation cannot be excluded. Longitudinal or cohort studies provide a stronger design to examine evidence in support of a causal association.

Evidence from Cohort studies

A 2007 systematic review identified 7 cohort studies investigating the association between cannabis use and schizophrenia, psychotic disorders or psychotic experiences (10). Since this publication, three more have been published. These 10 studies are described below and in Table 1.

Studies investigating psychotic disorder:

The Swedish Conscript Study found a dose-response relationship between cannabis use by age 18 and incident schizophrenia by age 45 (11, 12), with a 3-fold increase in risk in those who reported using cannabis more than 50 times by age 18 (95% CI 1.7, 5.5).

In the Dunedin birth cohort study (13) cannabis use by age 15 was associated with an increase in schizophreniform disorder at age 26 (OR 11.4, 95% CI 1.8, 70.5), with a weaker association in those first using between age 15 and 18 (OR 2.0, 95% CI 0.8, 5.0), although confidence intervals were wide and overlapping.

In the Dutch NEMESIS study (14) cumulative cannabis use was associated with incident psychotic outcomes measured 3 years later (OR 1.89, 95% CI 1.25, 2.85). A more recent study (15) extended these findings to also examine the risk of psychosis in ex-users of cannabis.

The California Hospital Study reported a large association between hospital admission diagnosis of cannabis use disorder and risk of later hospitalisation for schizophrenia (16) compared to a cohort of subjects who were hospitalised for appendicitis (HR 8.16, 95% CI 5.08, 13.12).

Studies investigating psychotic experiences

The Christchurch Health and Development study found evidence of an association between cannabis dependence and psychotic experiences after adjustment for numerous potential confounders (17, 18). The EDSP study found that any cannabis use at baseline was associated with psychotic symptoms 42 months later (19). In the ECA study (20) daily cannabis use was associated with increased risk of psychotic experiences, although there was little evidence that ever use of cannabis was associated with these experiences. In the NPMS (21) there was an association between cannabis dependence and incident psychotic

symptoms 18 months later in the unadjusted analysis, but this attenuated and CIs crossed the null after adjustment for confounders.

The Zurich study followed a sample of participants for 30 years (22), finding weak evidence that cannabis use was associated with schizophrenia nuclear symptoms prior to, but not after, adjustment. In the ALSPAC birth cohort, cumulative cannabis use at age 16 was associated with psychotic experiences at age 18 after adjustment for pre-birth and childhood confounders (23). After further adjustment for cigarette use and other illicit drug use this association attenuated to the null, though the authors discuss the difficulty of teasing out confounding versus mediating effects, as well as the potential problem of over-adjustment with such highly correlated measures.

The 2007 meta-analysis (10) reported a 40% increase in risk (95% CI 20-65%) of any psychotic outcome in cannabis users compared to never users, and a stronger association with heavier or more regular cannabis use (OR 2.1, 95% CI 1.5, 2.8), or in studies only looking at psychotic disorder (OR for ever use of cannabis 2.6, 95% CI 1.1, 6.1). Updating the estimate for ever-use of cannabis to include adjusted results from the Zurich Study and ALSPAC (Californian Hospital Study omitted due to the extreme nature of the exposure measure), results in a very similar updated pooled odds ratio for any psychotic outcome of 1.46 (95% CI = 1.24, 1.72; $p < 0.001$; $I^2 = 19\%$).

Interpretation of the findings

The results from these longitudinal studies show a consistent pattern of association between cannabis and psychosis, which could be indicative of a causal relationship. However, there are a number of reasons why the studies described above might have overestimated or underestimated the association between cannabis and psychotic outcomes, which we consider below.

i) Confounding

Residual confounding (i.e. over and above that accounted for in studies) would most likely lead to an overestimate of the true (causal) association, given that individuals who use cannabis regularly and those at higher risk of developing a mental illness share many similar characteristics. There is some evidence that residual confounding could still be present in

some of studies conducted to date, as studies of cannabis and psychosis that adjusted for more confounders showed greater attenuation of unadjusted estimates than those that adjusted for fewer, with attenuation of 60-80% of the unadjusted estimate in the 3 studies that adjusted most comprehensively for confounding (9). Given the wide range of confounders adjusted for across studies to date it is not clear what factors might be leading to residual confounding. However, as an example, few studies have adjusted for measures of early life attachment, abuse and trauma. Whilst measurement error in any variables adjusted for would lead to residual confounding, such error is particularly likely for measures pertaining to these constructs.

Shared genetic effects have also not been adequately adjusted for though it seems unlikely that this would explain the association observed given the small proportion of variance in cannabis use explained by common genetic variants for schizophrenia (24). A cross sectional study (25) reported an association between cannabis use duration and psychotic symptoms within sibling pairs, suggesting the association is not explained by genetic or shared environmental effects, whilst in the CHDS use of fixed-effects regression showed little effect of adjusting for unmeasured confounders that do not vary over time (though this does not account for unmeasured time-varying confounding) (17). However, a recent study (26) using a co-relative case-control design found that the association between cannabis disorder and schizophrenia became substantially smaller with increasing genetic relatedness from cousin-pairs to monozygotic twins, suggesting that estimates from population studies may be over-estimated due to genetic and shared environment effects.

ii) *Bias*

Given the long half-life of THC, heavy users of cannabis may be rarely un-intoxicated, which could lead to misclassification of psychosis outcomes, and bias in estimating the association with psychotic outcomes that are not due to the direct effects of exogenous cannabinoids. Studies that assessed hospitalisation for schizophrenia are unlikely to be substantially affected by this bias (12, 16). Furthermore, a study using the NEMESIS cohort investigated the association between cessation of cannabis use and persistence of psychotic experiences as a way of minimising intoxication effects (15) and found (weak) evidence for an increase in psychotic experiences in former users compared to never users. However, there were very few ex-users in this sample, and further studies are required to examine this further.

iii) Reverse causation

Most longitudinal studies conducted to date have attempted to account for reverse causation by excluding those with psychotic symptoms at baseline or adjusting for baseline symptoms. Whilst it is possible that prodromal symptoms at baseline were not picked up by screening and could have led to increased cannabis use, this seems unlikely, especially where studies restricted analyses to examine outcomes occurring after a likely prodrome effect (e.g. 12). Furthermore, studies examining the association between psychotic experiences and incident cannabis use show much weaker and less consistent evidence than those examining cannabis use and incident psychotic experiences (17).

Residual confounding, bias and reverse causation could have led to over-estimates of association. There are also a number of reasons why studies might have under-estimated true causal effects of cannabis on psychosis.

i) Misclassification bias

Assessing use of cannabis accurately is challenging, and relying on self-report almost certainly introduces measurement error. If misclassification was random across the cohort, this would likely lead to an underestimation of association. If differential misclassification occurred, results could have been underestimated, for example if people who went on to develop psychotic experiences were less likely to report illicit drug use due to suspicious (non-psychotic) beliefs at baseline. If, conversely, those who developed psychosis were more candid or likely to exaggerate about their drugs use at baseline (e.g. due to cognitive impairments or personality traits), findings may have been overestimated. Furthermore, cannabis comes in a variety of types and strains, which contain numerous cannabinoids aside from THC. As there is some evidence that cannabidiol (CBD) has anti-psychotic effects (27-29), the lack of information on relative ratios of THC:CBD in these studies means that self-reported use will not accurately reflect levels of psychoactive compounds reaching the brain; again measurement error, if non-differential is likely to lead to an underestimate of association. Misclassification may be reduced by use of biomarkers such as hair samples though these also have limitations in that they only index recent and heavy cannabis use, providing a less accurate measure of long-term cumulative use than self-report measures.

ii) Attrition

Longitudinal studies are prone to attrition as participants are lost to follow up. Participants who use drugs and those with mental health problems are both more likely to drop out of longitudinal studies, and this could lead to selection bias (a differential effect between exposure and outcome) that would underestimate effects of cannabis on psychosis (30, 31). Whilst the CHDS, NEMESIS and ALSPAC studies all attempted to model for attrition, and found no evidence that this impacted on the findings (14, 17, 23), these methods rely on a number of assumptions, and bias cannot be entirely excluded.

Identifying high risk groups

Even if the association between cannabis and psychosis is causal, cannabis is neither necessary nor sufficient to cause psychotic disorder; risk factors for multifactorial complex diseases are not deterministic (32). For this reason, studies have tried to identify sub-groups that might be at particularly high risk from cannabis use.

Age of use

In the Dunedin study, the authors stratified their findings by age of first use of cannabis (13), and found that participants who used cannabis by age 15 had a higher point estimate of association with schizophreniform disorder than those who used by age 18, suggesting the presence of a sensitive period of risk. However, CIs for the two groups overlapped substantially and were not directly compared, so findings are potentially consistent with sampling error. Furthermore, any difference, if present, could be driven by cumulative use: those who began using cannabis at an earlier age may have used cannabis more times by the time of the outcome measure than those who started using at a later age.

In the Swedish Conscripts study, the authors assessed risk of schizophrenia stratified by age of first use of cannabis, whilst taking in to account cumulative use of cannabis. They found no evidence for a difference in risk by age of first use (10).

There is some evidence from animal models that adolescence could be a critical period for development of the endocannabinoid system (33, 34). This system is involved in neuroplasticity and neurodevelopment, and cannabinoid CB1 receptor levels appear to fluctuate during adolescence in relation to brain development at this point (35). Therefore, whilst there is no strong evidence to support the hypothesis that cannabis is more harmful

to younger users, and that early adolescence is a sensitive period of risk, this remains an area of concern.

Genetic susceptibility

In the Dunedin cohort cannabis use was found to have a substantially stronger effect on the risk of schizophreniaiform disorder on those people homozygous for the valine allele at rs4680 (val¹⁵⁸met) within the catechol-o-methyl-transferase (*COMT*) gene than those homozygous for methionine (36). However, this interaction was only seen in participants who first used cannabis prior to, and not after, age 18, raising concern that this might be a spurious finding. None of eight studies published since then replicate this (e.g. see 37, 38). More recently an interaction has been reported (39), and replicated in one study, between cannabis use and *AKT1* on psychosis risk (40); however there are substantial concerns around gene environment interaction studies (38, 41), and currently evidence that effects of cannabis differ according to variation at *AKT1* is not robust.

Childhood trauma

Three studies have found that presence of both childhood trauma and cannabis use increased the *absolute* risk of psychosis to a greater degree than the sum of either risk factor alone (42-44). Although such findings could help inform which individuals are at higher risk of psychosis, such patterns of risk for co-exposure to two risk factors are the norm in multifactorial complex diseases (45, 46).

Strains of cannabis

A number of studies indicate that cannabis strains containing higher THC:CBD ratios may result in greater risk of psychotic outcomes, and that CBD might have anti-psychotic properties (27-29, 47). A recent case-control study found that whilst 'skunk' cannabis (high THC:CBD) was associated with risk of a psychotic episode, 'hash' cannabis (low THC:CBD) was not (48). This is an important emerging area of research, which could provide a target for campaigns if studies corroborate the finding that different strains of cannabis confer different risk of psychosis. However, given that studies conducted before skunk became widely used also showed an association between cannabis and psychosis, it is too early to assume that only skunk, but not lower potency forms of cannabis are associated with psychosis risk. Longitudinal studies of long-term effects of skunk versus hash, with accurate measures of THC and CBD are required, but will need to address the possibility that

participants are selecting to an extreme of use (heavy cannabis use in earlier studies, and stronger cannabis use as it became available) as a result of other characteristics that are (independently) associated with psychosis risk (49).

These studies have increased concern that as levels of THC in cannabis have altered over the past few decades (50-52), results from earlier studies could be underestimating the impact of the effects of cannabis on psychosis that exist today. Corroborating ecological evidence that psychosis risk has increased recently in young people exposed to higher THC than earlier birth cohorts has not been examined (53).

There is also increasing concern about the psychotogenic effects of synthetic cannabinoids, currently from case reports of individuals experiencing psychosis after using them (54). Given this, there is a strong need for more robust epidemiological studies to determine the likely impact of synthetic cannabinoids on risk of psychotic disorders.

Evidence in support of causation

There are a number of facets of the evidence presented above that are consistent with a causal association between cannabis and psychosis. The longitudinal, case-control and cross-sectional studies conducted to date have, for the most part, found consistent evidence of an association, even after adjustment for covariates. Those that assessed a dose-response relationship have found evidence for this. The experimental evidence showing that psychotic experiences occur during cannabis intoxication (1) indicates that cannabis has biological effects that could translate to chronic psychotic disorders. Neurobiological evidence on the effect of cannabis use, which includes dopaminergic, glutaminergic, and GABA activity modulation, are broadly consistent with the current understanding of neurobiology of psychotic disorders (55), as discussed in other articles in this issue (refs).

There is also indirect evidence that supports causality. For example, a number of studies (12-14), although not all (16, 23) found evidence for specificity of exposure, namely that associations between other drug use and psychosis are weaker than for cannabis. There is also some evidence of specificity of outcome (10, 56) though this is not seen in all studies (57).

Evidence inconsistent with a causal relationship

Given that cannabis use has increased greatly since the 1960s, an argument made against a causal association between cannabis and schizophrenia is that a corresponding increase in schizophrenia diagnoses has not been observed. Some studies have found that incidence of psychotic outcomes has increased in recent decades (58, 59), while others have found no change, or a decrease (60, 61). Ecological evidence such as this provides only very weak evidence for causality, as it cannot be ascertained whether individuals using cannabis are the same as those experiencing psychosis (the ecological fallacy), studies are unable to account for likely confounders, and do not account for other potentially competing risk factors for schizophrenia that may have declined over the same time period.

Addressing the uncertainty

With observational data there is always likely to be some uncertainty as to whether cannabis has a causal effect on chronic psychotic disorders such as schizophrenia. Although criteria often used to establish causality, including temporal distinction between exposure and outcome, strength and direction of association, biological gradient, consistency, specificity, coherence, experimental evidence, and biological plausibility are all met, there are examples in epidemiology where associations conforming to these criteria have turned out to be confounded when RCTs have been conducted (62).

Currently there remains a need for stronger evidence to address questions regarding the magnitude of causal effect on risk of psychotic disorders, the impact of different strains of cannabis, and to identify any groups at particularly high risk of developing psychosis following use of cannabis. Furthermore although we have only focused on positive psychotic symptoms in this article schizophrenia is also characterised by other clinical features such as cognitive impairment. Whilst cognitive deficits have also been shown to be associated with cannabis use (63) these studies suffer from the same issues as discussed above regarding establishing whether association from observational studies are causal or not.

Different epidemiological approaches may be required to help address these remaining uncertainties, particularly in relation to residual confounding. For example, it may be possible to conduct large, cluster-randomised trials to investigate long-term psychosis outcomes following substance use interventions. Although interventions are of limited efficacy and such trials are unlikely to be a pragmatic solution at present this may change as

more effective interventions are developed. Linkage of electronic registers to capture long-term outcomes from trial participants might also make such approaches more feasible in the future. Furthermore, as cannabis is legalised in some States of the USA, experimental studies of cannabis may become easier to undertake.

Observational studies across populations with differing underlying confounding structures (cross-cohort studies) may also help address questions of residual confounding. For example, breastfeeding, which is socially patterned in the UK but not in Brazil, was found to be associated with obesity only in the UK sample, whereas the association with IQ was observed in both the UK and Brazilian samples, indicating that the association with obesity is likely to be due to residual confounding, whilst that for IQ is more likely to be causal (64).

Mendelian randomisation, where genetic information is used as a proxy for an exposure of interest, could also be used as a method to minimise confounding (65). However, there are important limitations to Mendelian randomisation currently, in particular that genetic variants that robustly predict cannabis use have yet to be identified (65).

Implications

If the association between cannabis and schizophrenia is causal and of the magnitude estimated across studies to date (10), this would equate to a schizophrenia lifetime risk of approximately 2% in regular cannabis users (though risk for broader psychotic outcomes will be greater). This implies that about 98% of regular cannabis users will not develop schizophrenia, and therefore cannabis cessation interventions would need to prevent very large numbers from using cannabis in order to meaningfully effect incidence of schizophrenia. However, risk could be much greater in those at a higher genetic risk (66), or in those who use particularly potent strains of cannabis (48). For example, if regular cannabis use increased the risk of schizophrenia two-fold, and assuming the pattern of risk for co-exposure to cannabis and high genetic risk is approximately multiplicative, as it is for most risk factors for multifactorial complex disorders, then the lifetime risk in individuals with a first degree relative if they use cannabis regularly could be around 20%.

As cannabis exposure has increased then so should the attributable fraction of schizophrenia. From epidemiological studies to date, the population attributable fraction

(assuming causality) could be 10-25% depending on whether risk is confined to heavy cannabis or all users (10) . However, the absolute number of cannabis users needed to stop using cannabis in order to prevent one case of schizophrenia per year has been estimated at approximately 5000 for heavy users among men, and 10,000 to 15,000 among women (67). Given that current treatments for cannabis dependence have approximately 20% efficacy (68), these figures may need to be multiplied by five in order to give a meaningful number needed to treat. These figures will be lower if calculating risk of schizophrenia over the entire lifespan rather than over one year, and if considering broader psychosis outcomes (although most clinical interest is on severe outcomes where suffering is greatest). An effective public health campaign would be better placed trying to prevent people from taking up cannabis use or progressing to heavier use, than to stop current users, similar to tobacco prevention programmes (69).

There is no doubt that a public health message that cannabis use is harmful is appropriate. However clear communication of the risks of cannabis is needed, as a public health campaign that is ignored by those who it is aimed at has little value. Whilst it is important to avoid understating potential harms, which could put peoples' health at risk, it is also important to avoid overstating the harms of cannabis, which could lead to the message being ignored when experience does not match the warnings given.

Conclusion

Although there is always uncertainty when observational studies are relied on for evidence of causation, there is a strong body of epidemiological evidence to support the view that regular or heavy cannabis use increases the risk of developing psychotic disorders that persist beyond the direct effects of exogenous cannabinoids. However, in order to reduce uncertainty and obtain more accurate estimates of risk, multiple complementary techniques are required. Critically, cannabis exposure among adolescents and young people is common and psychosis remains rare – further evidence is required in order to characterise the population at greater risk of psychosis if exposed to cannabis. Only through robust converging evidence across neurobiology and observational epidemiology disciplines, including new techniques to better investigate causation from these data, can a clearer understanding of the relationship between cannabis and psychosis be elucidated.

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Table 1 Description of the longitudinal studies on cannabis and psychotic outcomes published to date

Cohort	Sample size (and with outcome)	Exposure	Outcome	Results (adjusted) OR(95% CI)	Strengths	Limitations
ECA (20)	2295 (477)	Daily use of cannabis (binary)	Psychotic experiences (binary)	2.0 (1.25, 3.12)	Large sample size, interview-based psychotic experiences measure	No attempt to account for intoxication
NEMESIS (14)	4045 (38)	Ever use and frequency of use	Psychosis symptoms (severity)	2.76 (1.18, 6.47)	Legality of cannabis use in Netherlands; investigation of self-medication hypothesis; attempt to remove intoxication effect; large sample size; repeated measures of exposure and outcome	Sample size too small to examine psychotic disorders robustly
Swedish cohort (12)	50087 (362)	Cumulative cannabis use	Schizophrenia diagnosis	Linear trend 1.2 (1.1, 1.4)	Large sample size, attempt to remove intoxication effect, schizophrenia measure	Only males included, therefore results may not be generalizable; large temporal gap between exposure and outcome, could miss variation in cannabis use; low

						levels of cannabis use at baseline
Dunedin (13)	759 (25)	Ever use of cannabis by age 15/18	Schizophreniform diagnosis	2.91 (1.20, 7.04)	Strong cohort retention, minimising possibility of attrition bias; schizophreniform disorder measure	Small sample size, exacerbated by dividing sample in to cannabis before/after 15; limited adjustment for confounding;
Christchurch (17, 18)	1265	Cannabis use; dependence	Psychotic experiences	1.8 (1.2, 2.6)	Thorough consideration of confounders; use of fixed-effects regression to minimize confounding by time invariant confounders	Lack of clinical measure of psychosis; small sample size.
EDSP (19)	2437 (424)	Used at least 5 times	Psychotic symptoms	1.2 (1.1, 1.3)	Investigation of reverse causation hypothesis;	Sample size too small to examine psychotic disorders robustly?
NPMS (21)	1795 (134)	Dependence (3-level measure)	Self-reported psychotic symptoms	1.5 (0.6, 3.9)	Thorough consideration of confounders	Few cannabis users; sample selected due to pre-existing mental health problems so may not be

						generalisable
Rosler (22)	591 [2200 (221) records]	Heaviness of use (3-level measure)	Schizophrenia nuclear symptoms (self-report)	Adjusted results not reported – unadjusted 1.77 (0.96, 3.24)	Many repeated measures over long follow up;	Small sample size; limited consideration of confounders
California (16)	41670 (174)	Hospitalisation for cannabis abuse	Hospitalisation for schizophrenia	8.2 (5.1, 13.1)	Large sample size;	Extreme exposure measure; limited consideration of confounders
ALSPAC (23)	1756 (97)	Cumulative use (4-level)	Psychotic experiences severity (4-level)	1.12 (0.76, 1.65)	Thorough consideration of confounders	Small sample size; correlation of covariates; young age of participants; lack of clinical measure of psychosis