F1000Reports MEDICINE

Published: 11 January 2013

Stronger evidence is needed before accepting that cannabis plays an important role in the aetiology of schizophrenia in the population

Suzanne H. Gage[1,2], Stanley Zammit[1,3] and Matthew Hickman[1]*

Addresses: [1]School of Social and Community Medicine, University of Bristol, Canynge Hall, 39 Whatley Road, Bristol, BS8 1TU; [2]MRC Centre for Causal Analyses in Translational Epidemiology, Oakfield House 15-23 Oakfield Grove, Bristol, BS8 2BN; [3]Institute of Psychological Medicine and Clinical Neurosciences, MRC Centre for Neuropsychiatric Genetics and Genomics, Cardiff University, Henry Wellcome Building, Heath Park, Cardiff, CF14 4XN

* Corresponding author: Matthew Hickman (matthew.hickman@bristol.ac.uk)

F1000 Medicine Reports 2013, **5**:2 (doi:10.3410/M5-2)

Abstract

Schizophrenia is a debilitating but poorly understood condition with very few known modifiable risk factors. Cannabis use can acutely induce psychotic experiences, but its causal relationship to schizophrenia is less well understood. Longitudinal cohort studies suggest that the association between cannabis and psychotic outcomes is not due to chance or reverse causation. However, the association could be due to bias or residual confounding. Methods that can test alternative explanations in greater depth are required. This is especially important as ecological studies have found little association between the increase in cannabis use over recent decades and incidence of psychotic disorders; public health models suggest that cannabis use may need to be treated and prevented in many thousands of users in order to prevent one case of schizophrenia. We believe that, while such uncertainty exists, there is a scientific duty to continue to investigate the role of cannabis in the aetiology of schizophrenia and that the policy case for considering cannabis exposure as a critical target for preventing schizophrenia is yet to be made. However, due to other evidence of the harms of cannabis use, this should not affect the public health message that cannabis can be harmful and that cannabis dependence should be prevented.

Introduction

Schizophrenia is a serious illness associated with substantial loss of quality of life, social and economic problems, co-morbidity and premature mortality, and the need to improve primary prevention is paramount [1,2]. Aetiology of schizophrenia offers few clearly modifiable factors: rates are higher in those with family history of psychiatric illness, men, and vary by migrant status and ethnic group, urbanicity and economic status [1-4]. Cannabis can cause acute transient, usually mild psychotic experiences while intoxicated, with minimal functional impairment directly following use [5], and can worsen the course of illness in people with schizophrenia [6]. The critical question, however, is whether cannabis use increases the risk of more severe and prolonged psychotic states such as schizophrenia, aside from these intoxication effects. If true, this could have important clinical and public health implications, as cannabis appears to be more readily modifiable than other factors for schizophrenia.

We consider the strength of the evidence for a causal relationship between cannabis use and chronic psychotic disorders, including schizophrenia, and how important

cannabis might be for public health and policy in terms of a target for prevention of these disorders.

Cannabis and psychosis

Evidence has been present for some years that individuals who use cannabis have an increased risk of psychotic outcomes. A systematic review of the longitudinal studies [7] found consistent empirical evidence that individuals who used cannabis had an increased risk of psychotic outcomes, and studies published since have also reported results consistent with these findings [8,9]. Although this suggests that the association is unlikely to be due to chance and due to the longitudinal nature of the studies, reverse causation (i.e. where the perceived cause-effect relationship may be reversed) is also unlikely - bias and residual confounding remain plausible explanations.

Considering confounding and bias

There are a variety of types of bias that could distort the relationship between cannabis and psychosis (as those subjects with both factors would be much more likely to drop out). Follow up bias, whereby people who use cannabis and people with psychotic symptoms may both be more likely to drop out of a cohort study, would be expected to lead to an underestimate of the relationship between cannabis and psychosis. Non-differential misclassification (i.e. where errors in the measurement of cannabis are unrelated to the outcome) of cannabis exposure would also dilute any relationship. Few of the studies, however, examine schizophrenia as an outcome, and conclusions regarding the effects of cannabis on this disorder are based primarily on studies of psychotic experiences [10]. Psychotic experiences occur much more commonly in the population than disorders such as schizophrenia and, in the majority of cases, do not lead to the distress or impairment that are universal characteristics of psychotic disorders. There are a number of lines of evidence indicating that psychosis exists on a continuum, and it seems reasonable to assume that risk factors for psychotic experiences in the general population will also be associated with risk for psychotic disorders. However, given the clear differences that exist between the epidemiology of psychotic experiences and that of schizophrenia, it may be invalid to infer the magnitude of the relationship between cannabis and schizophrenia from studies examining psychotic experiences as their outcome. Perhaps more importantly, however, acute psychotic episodes caused by intoxication effects may also bias findings. Not all longitudinal studies to date have considered intoxication effects, and where participants are using cannabis on a daily or regular basis, it seems unlikely that psychotic events induced by intoxication can be teased out at all. Studies of psychotic experiences in samples of the general population are likely to be particularly prone to outcomes resulting from intoxication effects compared with studies of clinical disorders diagnosed after periods of hospital admission, where such intoxication effects can be more readily excluded.

The main limitation to interpreting the association between cannabis use and schizophrenia has been that of residual confounding [10]. The cohort studies reviewed by Moore *et al*. [7] differ quite dramatically in the number and quality of confounders that are adjusted for. The studies that adjust for a large number of confounders find the point estimates attenuate to a greater degree (suggesting the size of the effect is smaller) than those that adjust for very few confounders. This suggests that there may still be residual confounding distorting the true relationship between cannabis use and psychotic symptoms. For example, few studies adjust for tobacco use, and other illicit drug use is only sporadically accounted for. It is also worth considering that drug taking of any kind could be associated with personality type or early-life and family adversity, which may be risk factors for psychosis, rather than the biological effect of any drug *per se*. Strategies attempting to address problems of confounding in observational studies include use of siblings as controls [11], use of statistical modelling methods, such as fixed-effects or self-controlled case series, which control for unmeasured time-invariant confounding [12,13] or use of mendelian randomisation (where genetic variants provide an unconfounded measure of exposure) and instrumental variable techniques if suitable measures become available [14,15].

Is the evidence good enough?

Observational epidemiology can suffer from spurious findings: bias, reverse causation or residual confounding have led to consistent results in observational studies, which are then shown to be false when investigated experimentally [16,17]. It is therefore important to consider evidence from other sources to complement (or test) observational epidemiological findings. One source of evidence that does not support a causal relationship between cannabis use and schizophrenia is the comparison of cannabis use and schizophrenia incidence over time. There is evidence that cannabis use in many developed countries has increased greatly over the past 40 years [18-20]. For example, in the UK, cannabis use has risen 10-20 fold since the 1970s [19]. However, recent data on new admissions for schizophrenia have shown no increase at all [18,21]; indeed, there is a suggestion of a downward trend in diagnoses.

A similar pattern of increasing cannabis use but stable incidence of schizophrenia is also seen in Australia [18].

However, these data are ecological, and therefore it is possible that relationships are due to different sub-populations driving the variations, or that improvements in mental health care or changes in other risk factors have reduced the risk of schizophrenia over this same time period (and confounded the relationship between cannabis and schizophrenia). The point is that there does not seem to be a simple observable relationship between cannabis exposure and schizophrenia incidence that would support substantial investment in a public health campaign to prevent schizophrenia through preventing cannabis use.

Does uncertainty in evidence matter?

Policymakers and clinicians invoke the "precautionary principle" to justify the importance of controlling and preventing cannabis use in relation to schizophrenia [22]. Even though it is not currently possible to be certain whether or not cannabis causes schizophrenia, there is a strong argument to encourage people not to use this drug [23]. For example, cannabis is most commonly used in the UK by smoking it with tobacco, which means it poses the same dangers that tobacco use does. As well as this, frequent cannabis use can lead to dependence and has been associated with impairments in educational, occupational and social attainments [9]. Nonetheless, although cannabis is a modifiable factor, estimates of the number of people that need to stop heavy cannabis use to prevent ***one*** case of schizophrenia are in the thousands (e.g. between 3000 and 5000 heavy cannabis users and between 10,000 and 20,000 young men and women with any cannabis use, respectively) [24]. Furthermore, current interventions to reduce dependence are of limited effectiveness, so for an intervention that was 20% effective, the "number needed to treat" would be in the tens of thousands. In terms of a public health message, there is no doubt that the potential harms from cannabis use should be highlighted, but even a large-scale campaign to reduce cannabis use may have a limited effect on reducing rates of schizophrenia.

It is possible that some individuals are at particularly high risk of developing a psychotic illness after using cannabis, and targeted interventions to reduce cannabis use in such individuals might be more successful than an *en masse* approach. A number of studies have tried to identify such high-risk individuals. For example, a report finding that the effect of cannabis on psychosis risk was strongly conditional on variation within the COMT gene [25] received a lot of interest amongst the scientific community, but this initial finding has not been directly replicated by any studies since [26-28]. It is perhaps in this area of high-risk subgroups in particular where evidence regarding the aetiological role of cannabis in schizophrenia is least robust.

Interest is also focusing on the strength of cannabis and whether different varieties of cannabis are more psychomimetic than others [29]. Whilst the delta-9-tetrahydrocannabinol (THC) component of cannabis can induce transient psychotic experiences [5], recent evidence suggests another component, cannabidiol (CBD), may actually be antipsychotic [30]. The strains of skunk (the cannabis most often used in the UK) that are most commonly available have very low CBD and higher levels of THC [31], and one study to date suggests that skunk may be associated with higher risk of schizophrenia than other forms of this drug [29]. However, the psychotogenic effects of compounds with different relative amounts of THC and CBD have not been wholly consistent in other studies [32,33].

Robust evidence is required to support the hypotheses that specific sub-groups are at particularly high risk of psychosis following cannabis use, or that differential effects of the THC and CBD components of cannabis are important in determining risk for schizophrenia. Assumptions based on weak evidence, or based on theoretical research paradigms, may be misleading. For example, as a strategy to reduce the harm related to tobacco use, individuals were encouraged to switch to "low tar" cigarettes with increased filter ventilation because machine-based research showed them to be less harmful than "high tar" varieties [34]. However, in practice, smokers responded by compensating for this: some blocked the filter with their fingers, and increased strength and frequency of inhalations, resulting in no health benefits from switching [35,36].

From a research perspective, research programmes directed at examining biological or psychological mechanisms by which cannabis might play an aetiological role in schizophrenia, or aimed at testing interventions based on such mechanisms are often costly to implement. Guidance of such programmes is dependent on high-quality evidence to increase the likelihood they will be cost-effective initiatives. At the moment, such evidence does not exist in the case for cannabis causing psychosis.

Conclusions

Despite consistent evidence that individuals who use cannabis have an increased risk of psychotic outcomes, it should not be surprising that the role of cannabis in the aetiology of schizophrenia remains uncertain given the limits of observational epidemiology. In particular, the extent to which the incidence of schizophrenia will be altered by reducing cannabis use or changing the type of cannabis used in the population, or in specific subgroups, remains unclear.

Whilst the evidence is "good enough" to continue promoting the public health message that cannabis is harmful, and that it may increase risk of schizophrenia, it is important not to overstate the evidence: the majority of people who use cannabis will not develop schizophrenia, and it appears that a considerable number of heavy cannabis users would need to be prevented in order to prevent one case of schizophrenia. From a scientific perspective, however, the extent to which use of cannabis leads to an increased incidence of schizophrenia, independently of confounding characteristics and separate from effects of chronic intoxication, remains uncertain. Whether preventing cannabis use will have any substantial impact on preventing psychotic disorders in the population, or within specific subgroups at risk, is yet to be adequately determined.

Abbreviations

CBD, cannabidiol; THC, delta-9-tetrahydrocannabinol.

Disclosures

The authors declare that they have no disclosures.

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