

4 Cannabis and schizophrenia: What does the research say?

There is consistent evidence from cross-sectional research—meaning research that is undertaken on a group of people at one point in time—that cannabis and psychotic disorders occur together more often than would be expected by chance ^{[129][130][131][132]}. Those in treatment for psychosis have high rates of cannabis use and cannabis use disorders (i.e. cannabis abuse and cannabis dependence) ^[133]. In the general population, individuals diagnosed as having a psychotic disorder have higher rates of cannabis use than those not diagnosed with a psychotic disorder ^{[130][92]}.

4.1 Why is cannabis suspected of causing psychosis?

Like amphetamines, cocaine and alcohol, the administration of large doses of cannabis (e.g. 60mg of cannabis resin oral) ^[134] and chronic heavy use ^[135] have been reported to cause psychotic symptoms lasting several hours in those without an existing psychotic disorder. Experimental trials ^{[136][137]} have shown that psychotic symptoms can appear with smaller doses (2.5–5mg intravenous and about 16.5mg oral respectively). These symptoms are temporary and do not persist without further use of cannabis. Early reports of cannabis psychoses that did not resolve did not adequately determine whether the individuals had prior psychotic episodes or risk factors ^[10].

The typical acute effects of cannabis resemble some of the features of schizophrenia, in particular the sensory distortions, inexplicable mirth, feelings of depersonalisation and loss of motivation. These resemblances have focused attention on the connection between cannabis use and schizophrenia even though the association between tobacco use and schizophrenia is of a similar strength, but without the apparently similar effects.

Similarly, temporary increases in psychotic symptoms after cannabis use are often noted in stable, medicated individuals living with schizophrenia ^{[138][56]}. Such transient effects of cannabis must be distinguished from chronic psychoses such as schizophrenia, although differential diagnosis of the acute syndrome may be difficult ^[139]. One of the reasons why the issue of the relationship between cannabis use and psychosis is so confusing is because of the lack of clear distinction between the association of cannabis use with transient psychotic symptoms, and with chronic disorders (such as schizophrenia) developed later on ^[10].

4.2 What is needed to investigate the causal association between cannabis use and psychosis?

The evidence of a cross-sectional association between cannabis use and psychosis is not enough to be able to conclude that cannabis causes psychosis. First of all, evidence of association does not provide information about the temporal relationship of the cannabis-psychosis relationship. It remains possible that experiencing psychosis could make it more likely that people go on to use cannabis ^[140]. Secondly, there may be a third factor that causes both cannabis use and psychosis. For example, the experience of an adverse life event may increase the likelihood of both cannabis use and schizophrenia. One method

of determining whether the cannabis-psychosis relationship is causal is to follow the same group of people (a cohort) over time. Cohort studies allow for the order of onset of cannabis and psychosis to be determined, and other factors that might affect drug use and psychosis to be measured from the outset. Studies with this design (“prospective cohort studies”) are reviewed below.

4.3 Major cohort studies: A review of the findings

4.3.1 Swedish Conscript Study

The first longitudinal study to find that cannabis use predicts subsequent development of psychosis was published almost twenty years ago, and was based on a sample of 45,570 male Swedish army conscripts. Conscripts were assessed at age 18 for a number of factors including substance use and psychiatric diagnosis. Hospital records for the next 15 years were examined to determine how many of these conscripts were admitted to hospital for schizophrenia ^[11].

Although most people treated for schizophrenia during the follow-up period did not use cannabis during adolescence, those who did use cannabis heavily (i.e. more than 50 times before the age of 18) were six times more likely to be hospitalised for schizophrenia by the age of 33 than those who had not used cannabis. Moreover, those who had used cannabis more than ten times (but less than 50 times) were three times more likely to be hospitalised for schizophrenia. However, these represent crude values that do not take confounding factors into account (see Appendix 1 for an explanation of these concepts). Once psychiatric factors, social and family background, and alcohol, tobacco and inhalant use were controlled for, the relative risk associated with being hospitalised for schizophrenia among those who had used cannabis at least ten times was reduced to just over two times and was no longer statistically significant. The adjusted relative risk for those who had used cannabis more than 50 times was not reported (for explanations of relative risks and odds ratios, including the concept of adjustment, see Appendix 1).

It should be noted that psychiatric diagnosis at baseline and having parents that were divorced were better predictors of schizophrenia than cannabis use. It is not possible to determine from the data whether cannabis use preceded psychiatric symptoms, or whether pre-morbid personality traits (i.e. personality traits that preceded cannabis use and development of schizophrenia) were responsible for both cannabis use and the development of schizophrenia.

In addition to the aforementioned limitations, the Swedish conscript study was criticised for not controlling for the use of other potentially psychotogenic (psychosis producing) substances such as amphetamines. A re-analysis of these data, which encompassed a longer follow-up period (27 years as opposed to 15 years), found that cannabis use remained predictive of schizophrenia in a dose-dependent manner even after accounting for other substance use and pre-morbid social integration ^[15]. Those who had used cannabis at least 50 times by age 18 were about three times more likely to be hospitalised for schizophrenia by the age of 45 than those who had not used cannabis. Overall, these studies showed that cannabis use during adolescence was associated with an increased risk of being hospitalised for schizophrenia over the next 27 years.

4.3.2 Epidemiological Catchment Area (ECA) Study

In the United States of America, a multi-site survey of the population was undertaken between 1980 and 1984 ^[92]. The Diagnostic Interview Schedule (DIS) was used to measure the presence of psychiatric disorders. This was administered at baseline, and at follow-up one year later. Substance use and social and demographic characteristics were also measured. To assess the risk associated with substance use and psychotic symptoms one year later, those with baseline psychotic symptoms (one or more positive responses to psychotic symptom items on the DIS) were excluded, and ‘cases’ (i.e. those who experienced at least one psychotic symptom at follow-up) were matched with ‘controls’ (i.e. those who did not report psychotic experiences at follow-up) on age. The age of the sample ranged between 18 and 49 years. A total of 477 cases were matched with 1,818 controls. Once social and demographic factors (e.g. gender, education, marital status, employment), baseline psychiatric disorders and other substance use (daily cocaine use, alcohol disorder) were controlled for, cannabis use was associated with a two-fold risk of experiencing psychotic symptoms. Put simply, this study suggests that daily cannabis use can double the risk of experiencing symptoms of psychosis.

4.3.3 Netherlands Mental Health Survey and Incidence Study (NEMESIS)

In the Netherlands, a population cohort of 4,045 males and females aged between 18 and 64 years was studied over three years from 1997 to 1999. It was found that those who reported any cannabis use at baseline (year one) were not significantly more likely to experience mild psychotic symptoms at follow-up three years later. However, they were almost 17 times more likely to report clinically significant psychotic symptoms and over 10 times more likely to be judged to need psychiatric care as a result of psychotic symptoms than those who had not used cannabis at baseline ^[141].

These results were found after controlling for age, sex, socio-economic status and other drug use. Additionally, the effect was dose-dependent, meaning that the higher the level of cannabis use, the greater the risk of experiencing significant psychotic symptoms. Importantly, none of those included in the sample had psychotic symptoms at baseline. Those who did show evidence of psychotic symptoms at baseline were studied separately, and the predictive effect of cannabis on subsequent psychotic symptoms was stronger than for participants who were symptom-free at baseline. This study suggests that cannabis use was associated with subsequent experience of clinically significant psychotic symptoms, and the greater the cannabis use, the stronger the association.

4.3.4 Dunedin Multidisciplinary Health and Development Study

The Dunedin Multidisciplinary Health and Development Study is a birth cohort that has been running in New Zealand since the 1970s. This study assessed childhood psychotic symptoms prior to cannabis use (age 11), cannabis use (defined as having used three times or more) at age 15 and 18, and schizophrenia symptoms and diagnosis of schizophreniform disorder at age 26, among 759 males and females born between 1972 and 1973 ^[12]. Schizophreniform disorder is similar to schizophrenia in terms of symptoms and signs but lasts for a shorter duration and does not necessarily lead to occupational or social problems ^[30]. It should be noted though, that the investigators in the Dunedin study used a conservative set of diagnostic criteria for schizophreniform disorder that required social and occupational problems.

Those who had used cannabis by age 15 had more symptoms of schizophrenia than those who had not used cannabis, even once other drug use and childhood psychotic symptoms were controlled for. Cannabis use at age 15, but not 18, was associated with schizophreniform diagnosis. However, this association did not remain significant once childhood psychotic symptoms were controlled for.

A recently published study using the Dunedin birth cohort data found that genetic predisposition moderated the effect of cannabis on psychosis. The gene of interest in this study coded for catechol-O-methyltransferase (COMT). The COMT gene product is involved in the metabolism of dopamine (the neurotransmitter thought to be involved in psychotic symptoms), and has been implicated in studies of the genetic basis of schizophrenia [86]. In the population, there are three allelic variants of this gene: Val/Val Val/Met and Met/Met [142]. It was found that adolescent cannabis users with a particular variant of the COMT gene (Val/Val, 25% of the sample) were at risk of developing schizophreniform disorder by the age of 26, whereas adolescent cannabis users who did not have this variant were not at an increased risk of schizophreniform disorder [86]. Interestingly, Suzuki et al. [143] reported a similar association of vulnerability to the recurrence of methamphetamine psychosis with this allelic variation.

The variants of the genes in and of themselves—that is, irrespective of cannabis use—were not associated with diagnosis of schizophreniform disorder. Moreover, participants with the Val/Val allele who did not start using cannabis until adulthood were not at an increased risk of schizophreniform disorder. The authors argued that this could indicate that the increased risk of psychosis among those with the particular variant of the gene is conditional on the presence of an environmental risk factor (in this case, adolescent cannabis use). The authors suggest that there may be a sensitive period of brain development during adolescence, or that the adult-onset cannabis users had not used cannabis for long enough for the psychotogenic effect of cannabis to take effect.

The significant interaction between adolescent cannabis use and the Val/Val allele remained significant once childhood psychotic symptoms, cannabis use during adulthood, other drug use and conduct disorder were controlled for. Replication of this result is needed before any strong conclusions can be drawn [144], but the data suggest that cannabis use in adolescence may interact with genetic vulnerability to lead to the development of a psychotic disorder. The importance of pre-existing vulnerability to psychosis is also seen in the earlier study [12], which found that there was no association between cannabis use and schizophreniform disorder once childhood psychotic symptoms were controlled for.

4.3.5 Christchurch Health and Development Study

The Christchurch Health and Development Study, another New Zealand birth cohort started in the 1970s, has recently reported results supporting a causal link between cannabis and psychotic symptoms [13]. Ten questions from the Symptom Checklist 90 (SCL-90), which is a measure of general psychiatric distress, were chosen to be representative of psychotic symptoms [145]. These items were administered to the 1,055 participants at age 18, 21 and 25 years to determine psychotic symptoms experienced during the month preceding the interview. This study controlled for a wide variety of possible confounding factors, including prior history of psychotic symptoms and cannabis use, other psychiatric diagnosis (previous

and current), other substance use disorders, adverse life events, deviant peer affiliations, family socio-economic status, family functioning, child abuse, IQ and individual personality characteristics, as well as fixed unmeasured factors—such as genetic factors—which were controlled through statistical modelling. Increasing rates of cannabis use were associated with increasing rates of psychotic symptoms. Daily cannabis users had rates of psychotic symptoms that were between 1.6 and 1.8 times higher (depending on factors controlled for) than non-users of cannabis. The statistical analysis indicated that cannabis use increased the number of reported psychotic symptoms, rather than the other way around.

4.3.6 Early Developmental Stages of Psychopathology Study

The Early Developmental Stages of Psychopathology Study assessed a population-based sample of 2,437 German adolescents and young adults at baseline, and then four years later^[14]. Predisposition to psychosis was measured using the SCL-90, and psychosis outcome was defined as at least one (broad psychosis outcome) or two (narrow psychosis outcome) positive responses to the 15 core psychosis items in the composite international diagnostic interview (CIDI). After controlling for age, sex, socio-economic status, childhood trauma, other drug use and predisposition to psychosis, those who used cannabis at least five times at baseline were somewhat more likely to experience any psychotic symptom four years later than those who had not used cannabis. Further analysis indicated that the association occurred in a dose-response manner. The effect was stronger for those who were predisposed to psychosis at baseline than those who lacked such a predisposition. The effect was also stronger for the narrow psychosis outcome than for the broad outcome. Importantly, predisposition to psychosis did not predict cannabis use four years later. Overall, the study suggests that cannabis use among adolescents and young adults who used cannabis were just under two times as likely to experience psychotic symptoms four years later, compared with those who did not use cannabis. The risk was increased for those who used cannabis frequently, and for those who were vulnerable to psychosis.

4.3.7 National Psychiatric Morbidity Survey

In Great Britain a sample representative of the general population were interviewed for the presence of psychiatric disorders using the Clinical Interview Schedule—Revised (CIS-R). Participants who had a mental health disorder or neurotic symptoms at baseline, as well as a random sample of 20% of participants who did not have a mental health disorder were followed up 18 months later^[91]. At baseline and follow-up the Psychosis Screening Questionnaire (PSQ) was used to measure psychotic symptoms. Individuals with a psychotic disorder at baseline were excluded from the sample analysed, leaving a sample of 1,795. Cannabis dependence at baseline was related to psychotic symptoms at follow up. However, after sociodemographic variables, drug use and psychiatric morbidity were controlled, neither of the cannabis use variables (used cannabis in the year prior to baseline and baseline dependence on cannabis) were related to psychotic symptoms. Four other variables were related to an elevated risk for psychotic symptoms: living in a rural area, lack of social support, and adverse life events. This study did not find that cannabis use or dependence was related to an increased risk of experiencing psychotic symptoms, among a general population cohort of adults.

Table 4.1: Cohort studies on cannabis use and psychotic disorders & symptoms

Authors (Year)	Sample	Cannabis use measure	Outcome (measure)	Controls	Adjusted odds ratio (95% CI)
SYMPTOMS					
Tien and Anthony (1990)	2,295 American adults, aged 18–49	Daily use of cannabis at baseline	Experienced at least one psychotic symptom one year later (DIS)	Psychiatric diagnosis at baseline, age, gender, education, marital status, employment, alcohol use disorder, daily cocaine use, psychotic symptoms at baseline.	2.0 (1.2–3.1) (relative risk)
van Os et al. (2002)	4,104 Dutch males and females from population sample, aged 18–64	Used cannabis at baseline	a) Low-level psychotic symptoms (BPRSa) 3 years later b) Pathological-level symptoms (BPRS)	Age, gender, ethnic group, marital status, education, urban dwelling, discrimination, other drug use. Those with psychotic symptoms at baseline excluded.	a) No significant effect b) 16.9 (3.3–86.1)
Fergusson et al. (2005)	1,055 New Zealander males and females from Christchurch birth cohort	Daily cannabis use in year prior to ages 18, 21, and 25	Psychotic symptoms in past month at age 18, 21 and 25 (SCL-90c)	Other drug dependence, gender, IQ, parental criminality.	1.6 (1.2–2.0)
Henquet et al. (2005)	2,437 German males and females from population sample, aged 14–24	Used cannabis at least 5 times at baseline	Any psychotic symptoms 4 years later (M-CIDId)	Baseline use of other drugs, predisposition to psychosis, age, gender, socioeconomic status, urban dwelling, childhood trauma.	1.7 (1.1–2.5)
Wiles et al. (2006)	1,795 British males and females from the general population	Used cannabis in the year prior to baseline, or dependence on cannabis	Incident psychotic symptoms during the 18 month follow-up period (Psychosis Screening Questionnaire)	Age, gender, area of residence, social support, adverse life events, alcohol and tobacco use, marital status, IQ. Individuals with a psychotic disorder or psychotic symptoms at baseline were excluded.	No significant effect

Authors (year)	Sample	Cannabis use measure	Outcome (measure)	Controls	Adjusted odds ratio (95% CI)
DISORDERS					
Andreasson et al. (1987)	45,570 Swedish male conscripts, aged 18	Used cannabis more than 10 times by age 18	Hospital admission for schizophrenia 15 years later at age 33 (hospital records)	Psychiatric diagnosis at age 18, social & family background, school adjustment, tobacco, alcohol and solvent use.	No significant effect after adjustment
Zammit et al. (2002)	50,053 Swedish male conscripts, aged 18	Used cannabis more than 50 times by age 18	Hospital admission for schizophrenia 27 years later at age 45 (hospital records)	Psychiatric diagnosis at age 18, IQ, social integration, disturbed behaviour, tobacco use, place of upbringing, other drug use.	3.1 (1.7–5.5)
van Os et al. (2002)	4,104 Dutch males and females from population sample, aged 18–64	Used cannabis at baseline	Need for treatment (judged by clinicians)	Age, gender, ethnic group, marital status, education, urban dwelling, discrimination, other drug use. Those with psychotic symptoms at baseline excluded.	10.5 (1.8–63.2)
Arsenault et al. (2002)	759 New Zealander males and females from Dunedin birth cohort	Used cannabis at age 15, continued use at age 18	DSM-IV diagnosis of schizophreniform disorder at age 26 (DIS)	Gender, socioeconomic status, psychotic symptoms prior to cannabis use.	No significant effect
Caspi et al. (2005)	803 New Zealander males and females from Dunedin birth cohort	Used cannabis by age 15 or used regularly at age 18	DSM-IV diagnosis of schizophreniform disorder at age 26 (DIS)	Use of other drugs, childhood psychotic symptoms, IQ, conduct disorder.	10.9 (2.2–54.1) with genetic vulnerability, no association for those without such vulnerability

Abbreviations:BPRS = *Brief Psychiatric Rating Scale*DIS = *Diagnostic Interview Schedule*SCL-90 = *Symptom Checklist 90*M-CIDI = *Munich version of the Composite International Diagnostic Interview*

4.4 What do these cohort findings say about the link between cannabis and psychosis?

The cohort studies reviewed here all report associations between cannabis use and subsequent indicators of psychosis, and the association often occurs in a dose-response manner. These results, combined with the cross-sectional evidence for association and biological plausibility, argue that cannabis use, particularly early and frequent cannabis use, is associated with later psychosis. Existing reviews of this issue have concluded that the evidence from these cohort studies show that cannabis use has a causal relationship to psychosis ^{[18][146][147]}. However, most of the studies measure psychotic symptoms rather than diagnosed psychotic disorders (see Table 2.1); the latter have more significance clinically. Of the studies that did measure disorders, only one found a relationship between cannabis and hospitalisation for schizophrenia ^[15]. Whether this can be generalised to the population is uncertain, as an interaction between cannabis use and the stress of military duty on emerging schizophrenia is not implausible ^[117]. Another found a relationship between cannabis and schizophreniform disorder, but only for those participants with a particular genetic variant ^[86]. Another found a relationship between cannabis use and the need for treatment associated with psychotic symptoms, but the confidence intervals were imprecise ^[141]. These and other methodological issues have led to difficulties in definitively stating that cannabis use causes ongoing psychotic disorders. In a recent, comprehensive meta-analysis of the relationship between cannabis and psychosis ^[148] the authors addressed this issue of psychosis outcome and the relationship persisted. With the application of more stringent statistical methods, it was concluded that heavy cannabis use (e.g. more than 50 uses before the age of 18) was associated with about twice the risk of any psychotic outcome when compared to no use.

4.4.1 Problems with using psychotic symptoms as an outcome measure

A number of important limitations are evident in using psychotic symptoms as a proxy for psychosis. In the Christchurch study, for example, psychotic symptoms were measured using ten items from the SCL-90, from both the 'psychoticism scale' and the 'paranoid ideation' scale. Some studies suggest that the psychosis and paranoid scales of the SCL-90 do not successfully identify psychotic patients in clinical samples, and that participants who are not psychotic may be found to have elevated scores on the psychotic symptom dimension ^[149]. It has also been argued that this instrument (administered in full) should be used as a global measure of psychological distress rather than a measure of symptoms of particular disorders ^{[150][151]}. In the Christchurch study, the average number of symptoms endorsed by daily cannabis users was less than two, and it was unclear whether the particular symptoms measured via the SCL-90 actually measured the cardinal symptoms of serious psychotic disorders (e.g. 'Hearing voices that other people do not hear'), or other symptoms of schizophrenia that are not specific to DSM-IV diagnosis of schizophrenia (e.g. 'Feeling that other people cannot be trusted' or 'The idea that something serious is wrong with your body') ^[30]. The clinical significance of endorsing one or two symptoms is unclear, particularly when the pattern of symptoms endorsed in those participants who were frequent users of cannabis was not specified ^[152]. Three other studies, the ECA, EDSP and British Psychiatric Morbidity study, only measured psychotic symptoms; similar limitations apply in terms of determining the clinical significance of these symptoms. It is also possible

that cannabis users, due to familiarity with drug-induced experiences that are similar to psychotic symptoms (“Hearing voices that other people do not hear”) and discourse with other users about such symptoms, may be more willing to report them. This may be particularly pertinent for psychotic symptoms that many people experience, but are reluctant to disclose ^{[153][90]}.

One of the major strengths of the Swedish and Dunedin studies was that the outcome measures—hospital admissions for schizophrenia, and diagnosis of schizophreniform disorder, respectively—were clear and quantifiable in terms of clinical and public health significance. Although the Dutch NEMESIS study measured psychotic symptoms associated with the need for psychiatric care (judged by a panel of professionals), the number of participants who experienced psychosis that warranted treatment was very small (n=7), leading to large confidence intervals.

4.4.2 Reverse causality: The self-medication hypothesis

Cannabis and psychosis may be associated because those who develop a psychotic disorder use cannabis in an attempt to alleviate their symptoms; in other words, to ‘self-medicate’ ^[49]. The temporal correspondence between the age at which psychological problems associated with schizophrenia typically appear ^[154] and the average age of first use of cannabis and other drugs ^[155] adds to the attractiveness of this model. The prospective design of the longitudinal cohort studies employed specific methods to rule out the self-medication hypotheses, including ^[13]; exclusion of those with any history of psychotic experiences in the follow-up study ^[141]; and assessing whether predisposition to psychosis is predicted by later cannabis use ^[14]. These methods cannot rule out that individuals who are developing a psychotic disorder may use cannabis to alleviate some of the symptoms they experience ^[156]. Although it is generally accepted that the self-medication hypothesis is not the major explanation for the relationship between cannabis and psychosis ^[147], it has been reported that schizotypal symptoms precede cannabis use in some cases ^[157]. A recent Australian study of a group of patients with psychotic disorders found that a bidirectional relationship exists between cannabis use; cannabis use predicted psychotic symptom relapse, and psychotic symptoms predicted cannabis use relapse, independent of medication and other drug use ^[158]. Overall, while the evidence for self medication of psychotic symptoms with nicotine is substantial, it is considerably weaker for cannabis.

4.4.3 Control of confounding factors

A major strength of both the Christchurch and Dunedin studies is the birth cohort design, which allows for a wide range of early childhood and family risk factors to be measured and controlled for. The Dunedin study was the first study to measure and control for psychotic symptoms in childhood, before the advent of cannabis use. Importantly, the predictive association between adolescent cannabis use and schizophreniform disorder was no longer significant once early psychotic symptoms were controlled for, suggesting that the association between cannabis use and schizophreniform disorder could be explained by existing vulnerability to psychosis. Alternatively, failure to identify a significant relationship may have been due to the small number of participants who were diagnosed with schizophreniform disorder (n=25). Other studies, particularly the ECA, the British survey and

the NEMESIS study, did not measure early childhood and family risk factors as rigorously as the New Zealand studies. The implication of this is that factors that may be related to both cannabis use and psychosis, and may account for the relationship—such as adverse events in childhood—could not be controlled.

Another important variable that is controlled in most, but not all studies, is baseline psychotic symptoms. While the Swedish conscript study assessed psychiatric symptoms and controlled for psychiatric disorders at baseline, it is uncertain whether the psychiatric symptoms recorded were used in the analysis. If this was the case, it would support the conclusion that the limited assessment of social integration satisfactorily controlled for early signs of schizophrenia.

4.4.4 The importance of psychosis vulnerability

Pre-existing vulnerability to psychosis appears to be an important factor that influences the link between cannabis use and psychotic disorders according to the studies reviewed here. The Dunedin data showed that once childhood psychotic symptoms were controlled, cannabis use no longer predicted development of schizophreniform disorder, although the association between cannabis and psychotic *symptoms* persisted ^[12]. The Dunedin cohort data are also suggestive of a potential genetic vulnerability to the psychotogenic effect of cannabis ^[86]. However, vulnerability to psychosis has not been measured in many of the studies reviewed here ^{[11][92][91]}. Unmeasured vulnerability to psychosis or other unmeasured psychiatric problems may play a role in later cannabis use, and this should be assessed or controlled for in future studies on the relationship between cannabis and psychosis ^[20]. Other studies (not reviewed here) also support the importance of psychosis vulnerability in the effect of cannabis on psychotic disorders ^[159].

4.4.5 Measurement of cannabis and other drug use during the follow-up period

A major limitation of the Swedish study was that there was no measure of cannabis use (or other drug use) during the 27-year follow-up period. It remains possible that those who used cannabis at age 18 were more likely to use other psychotogenic (i.e. psychosis inducing) substances such as amphetamines subsequently. This objection is partially answered by the result that amphetamine use at baseline did not affect the relationship between cannabis use and later hospitalisation ^[15].

4.5 Is the evidence sufficient?

Although the studies reviewed here found a relatively consistent relationship between cannabis and various measures of psychosis, only two of the studies reported a significant relationship between cannabis use and the subsequent development of a psychotic *disorder* meeting diagnostic criteria, once confounding factors were controlled for. The population impact of experiencing one or two *symptoms* of psychosis—particularly when it is often unclear whether the symptoms occurred within the period of cannabis intoxication—is unclear. However, it is obvious that the experience of psychotic symptoms is strongly connected to a subsequent psychosis ^[80].

In what ways might cannabis influence the development of schizophrenia? The notion that cannabis is sufficient to cause schizophrenia is unlikely to be correct. Even psychotic episodes precipitated by large doses of cannabis almost always resolve with detoxification, and few frequent and/or heavy cannabis users are ever diagnosed with schizophrenia. It seems likely that cannabis interacts with a variety of risk factors, from genetic to personality variables ^[160], perhaps over some years. In combination with strong risk factors like a genetic predisposition, even modest cannabis or other psychoactive drug use may be sufficient to precipitate schizophrenia. Where the other risks are weaker, a gradual decline to heavy cannabis use related to the known danger of using cannabis to cope with negative mental states and poor social interaction may be more plausible (e.g. ^[161]). It must be remembered that this applies to other drugs such as alcohol and amphetamines, and especially to polydrug use.

4.5.1 Can cannabis cause schizophrenia that would not have otherwise occurred?

Given the evidence presented above, it is clear that prior cannabis use and schizophrenia co-occur often enough to suggest a causal relationship, and that what we know about schizophrenia and the effects of cannabis are broadly consistent with causal models. Whether another factor is causing both schizophrenia and cannabis use is uncertain. Several studies have presented evidence that prodromal (pre-clinical) symptoms precede both schizophrenia and cannabis use and argue that the effect of these symptoms on cannabis use is sufficient to explain the relationship between such use and eventual schizophrenia. This seems to be the best fit between the causal models presented above and the accumulated evidence. It is still possible that cannabis or other drug use may precipitate schizophrenia in vulnerable individuals who would otherwise have not developed it ^[162], thus leading to new cases of psychosis.

Despite a rise in the prevalence of cannabis use in the population internationally over the last three decades ^[2], most studies of the incidence of schizophrenia over that time report either no change ^[163], or a decrease ^{[164][165]} (for a review, see Munk-Jørgensen ^[166]). It has been generally accepted that the incidence of psychosis and schizophrenia has not changed since the 1970s in Australia ^{[167][1]}. If this is the case, then cannabis use may not be causing an increase in psychotic disorders. The fact that the prevalence of cannabis use in Australia is substantially higher than that worldwide should make this effect easier to observe.

However, detecting changes in the incidence of psychiatric disorders is not a straightforward task; increases or decreases may be accounted for by changes in how a disorder is diagnosed, changes in the likelihood of a diagnostic record being available to researchers, or changes in the demographics of the population, such as decreases in the proportion of young people ^[164]. Indeed, the low incidence of schizophrenia may obscure minor changes in that incidence.

A relatively recent study from the United Kingdom examined the incidence of schizophrenia by assessing hospital admissions in an area of London between 1965 and 1997. Standard diagnostic criteria were applied, and population variations were taken into account ^[168]. The incidence of schizophrenia increased from 6.8 per 100,000 between 1965 and 1968,

to 15.3 per 100,000 population between 1993 and 1997. This increase in incidence was greater for young people, and occurred mostly in the 1980s and 1990s. A study using the same data found that cannabis use in the year prior to first presentation for psychiatric treatment increased from 1965 to 1999 among all patients ^[169]. This increase in cannabis use over that period is expected, given general population trends over this time, but the study found that those presenting with schizophrenia had a greater increase in cannabis use than those presenting for other non-psychotic psychiatric problems. Although there were some limitations of this study (e.g. no general population comparison group, no control for confounding factors that may have been related to cannabis use and schizophrenia such as other substance use), the studies are consistent with cannabis use contributing to schizophrenia.

It has been suggested that cannabis use may simply accelerate the onset of schizophrenia ^{[86][170]}, instead of causing new cases. Age of onset in schizophrenia has become lower over the last three decades ^[171], and cannabis users have been found to be younger at the onset of the first psychotic episode than those who have not used cannabis ^{[172][114]}. This may be of clinical importance as earlier age of onset of schizophrenia is associated with poorer prognosis ^[172].

In summary, there is no convincing evidence of an increase in the incidence of schizophrenia over the last three decades in Australia. The contentious issue of whether cannabis use can cause serious psychotic disorders that would not otherwise have occurred cannot be conclusively answered, although the available evidence strongly suggests that some such cases have occurred.

4.6 How does cannabis compare to other risk factors for schizophrenia?

4.6.1 Relative strength of risk factors

Genetic factors confer a greater risk of schizophrenia than the environmental factors just discussed, including substance use ^[77]. Because the exposure to other risk factors in the population is relatively higher (e.g. many more people are exposed to an urban environment than to the inheritance of genes from parents who had been diagnosed schizophrenia) the resulting number of cases of schizophrenia may be larger. Therefore, the population attributable risk (PAR) is larger, as shown in Table 4.2 ^[125].

As has been outlined in this review, there are numerous risk factors that potentially contribute to the aetiology of psychotic disorders. Most studies have focused on the risk factors associated with schizophrenia. How do they compare with one another? A study of a population-based cohort in Denmark compared the relative risks and population attributable risks associated with a variety of factors related to schizophrenia ^[125]. The table below presents their findings, along with the odds ratio associated with the risk of schizophrenia for those who used cannabis more than ten times during adolescence from the Swedish Conscript study ^[15]. Both studies used hospitalisation for schizophrenia as the outcome.

Table 4.2 Risk factors for schizophrenia: Relative Risk and Population Attributable Risk

Risk factor	Relative Risk	Population Attributable Risk (%)
One or both parents with schizophrenia	7.2–46.9	3.8
One or more siblings with schizophrenia	7.0	1.9
Used cannabis more than 50 times by age 18 ^a	3.1 ^b	8.0
Urban place of birth	2.4	34.6
Season of birth	1.1	10.5

Values from Mortensen et al. (1999), except ^a, which is from Zammit et al. (2002)

^b Odds ratio

Family history of schizophrenia was associated with the greatest relative risk for subsequent hospitalisation for schizophrenia; having a father (RR = 7.2; 95%CI = 5.1–10.2), mother (RR = 9.3; 95%CI = 7.2–11.96) or both parents (RR = 46.9; 95%CI = 17.6–125.3) affected greatly increased the likelihood of schizophrenia in a child [125]. The factor with the smallest relative risk was season of birth (RR: 1.1; 95% CI: 1.06–1.18). However, if a large proportion of the population is exposed to such a risk factor, the number of cases can be substantial [124]. The population attributable risk (PAR) is an estimate of the percentage of cases due to one or more risk factors. Mortensen and colleagues (1999) also calculated the PAR for the risk factors, and found that the factor with the highest PAR was place of birth, accounting for 34.6% of hospitalisations for schizophrenia. Season of birth is now the second most significant risk factor, accounting for 10.5% of hospitalisations, but this is for a location in the Northern Hemisphere. Relatively heavy cannabis use in adolescence was the third most significant risk factor for schizophrenia in terms of both measures.

To apply the criteria for a causal association mentioned above, while cannabis use is associated with a diagnosis of schizophrenia, the association is modest. The temporal precedence of cannabis use in schizophrenia is disputed by some research [157] and the same strand of research provides an alternative mechanism for the association. The argument for cannabis as a causal factor in schizophrenia is strengthened by the similarity of some of its effects to the symptoms of psychosis and the common factors acting in other acute drug-induced psychoses. In contrast, an attempt to distinguish characteristic patterns of symptoms of schizophrenia between cannabis users and non-users was unsuccessful [173].

It should also be noted that PAR values can be misleading, particularly when the outcome may be the result of multiple causes [174], as is the case with schizophrenia [77]. The amount of variation in the reported PAR between studies is considerable, raising questions about the meaningfulness and accuracy of any single figure taken in isolation. For an attributable risk ratio to be valid, the influence of other risk factors (e.g. other drug or alcohol use) must not be affected by the elimination of the risk factor in question (i.e. cannabis use). This may not be the case, as decreasing cannabis use could lead to increased use of alcohol or other drugs. Benichou [174] suggests that a weaker interpretation of attributable risk may be appropriate in such scenarios, such that the PAR represents the proportion of the disease that can be linked, rather than attributed, to the exposure.

4.6.2 How does cannabis compare to other drugs?

As mentioned previously, the use of other recreational drugs often precedes the onset of schizophrenia, particularly when more than one drug is used. As an example, the abuse of amphetamines is known to be associated with emerging psychosis, both acute and chronic [99]. The action of amphetamines upon dopamine activity is well known, and both dopaminergic activity and psychotic symptoms increase in those with schizophrenia when amphetamines are administered [175]. However, the lower prevalence of use of amphetamines (see Figure 2.1) makes it difficult to compare the extent to which that use contributes to schizophrenia compared to cannabis.

4.7 What is the underlying mechanism?

If cannabis use exacerbates psychotic symptoms, or triggers the onset of a psychotic disorder, a plausible biological mechanism would aid the understanding of its effect.

The cannabinoid Δ^9 -tetrahydrocannabinol (THC) was characterised in the 1960s, but for the next 20 years, it was unclear how THC exerted its effect on the brain [4]. In 1988, endogenous THC-binding receptors were reported [176]. Soon after, a naturally occurring cannabinoid (termed an 'endogenous cannabinoid', or an 'endocannabinoid') was identified in the brain—anandamide [177]. Since then, several other endocannabinoids have been discovered [4]. It is these discoveries that have made the investigation of how cannabis may be related to psychosis possible.

There are several main lines of evidence suggesting that it is biologically plausible that cannabis is involved in the occurrence of psychotic symptoms. Firstly, high concentrations of cannabinoid receptors (binding sites) in the brain are found in areas of the brain that are thought to be linked to schizophrenia, such as the hippocampus [178][179]. Secondly, cannabis receptors appear to be important in modulating the activity of dopamine, which is thought to be involved in psychosis [180]. Thirdly, the endogenous cannabinoid system may be abnormal in those living with schizophrenia, such that levels of endocannabinoids, like anandamide, are elevated in those with psychotic disorders [181], and this may be a response to psychosis [182]. In contrast, a more recent study [183] has found that frequent cannabis use may reduce this anandamide activity, providing a mechanism for the exacerbation of psychotic symptoms by cannabis. Finally, a gene for a cannabinoid receptor in the brain has been found to be associated with a specific type of schizophrenia [184], although not all studies have found an association [185].

4.8 Conclusion

Evidence implicating cannabis use in the aetiology of schizophrenia has accumulated in the past 20 years. The conflicting nature of this evidence and its restricted generalisability argues for caution in assuming that cannabis use can cause schizophrenia. Nonetheless, there appears to be a sound basis for informing current and potential cannabis users of the potential risks. This applies with even greater force to those individuals with known or suspected vulnerabilities to schizophrenia.

Key points: Cannabis and schizophrenia

There are many factors that contribute to the emergence of psychotic disorders such as schizophrenia.

- There is good evidence that cannabis makes some symptoms of psychosis transiently worse.
- The evidence that the association of cannabis use with emerging psychosis is due to self-medication is not conclusive.
- Cannabis use increases the risk of schizophrenia among those with other risk factors.
- While it is likely that cannabis use leads to cases of schizophrenia that would not have occurred otherwise, the number of such cases is probably small.