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Cannabis as a risk factor for psychosis: systematic review

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Abstract

Various lines of evidence suggest an association between cannabis and psychosis. Five years ago, the only significant case–control study addressing this question was the Swedish Conscript Cohort. Within the last few years, other studies have emerged, allowing the evidence for cannabis as a risk factor to be more systematically reviewed and assessed. Using specific search criteria on Embase, PsychINFO and Medline, all studies examining cannabis as an independent risk factor for schizophrenia, psychosis or psychotic symptoms, published between January 1966 and January 2004, were examined. Additional studies were also reviewed from references found in retrieved articles, reviews, and a cited reference search (ISI-Web of Science). Studies selected for meta-analysis included: (i) case–control studies where exposure to cannabis preceded the onset of schizophrenia or schizophrenia-like psychosis and (ii) cohort studies of healthy individuals recruited before the median age of illness onset, with cannabis exposure determined prospectively and blind to eventual diagnosis. Studies of psychotic symptoms were also tabulated for further discussion. Eleven studies were identified examining the relationship between cannabis use and psychosis. Seven were included in the meta-analysis, with a derived odds ratio (fixed effects) of 2.9 (95% confidence interval = 2.4–3.6). No evidence of publication bias or heterogeneity was found. Early use of cannabis did appear to increase the risk of psychosis. For psychotic symptoms, a dose-related effect of cannabis use was seen, with vulnerable groups including individuals who used cannabis during adolescence, those who had previously experienced psychotic symptoms, and those at high genetic risk of developing schizophrenia. In conclusion, the available evidence supports the hypothesis that cannabis is an independent risk factor, both for psychosis and the development of psychotic symptoms. Addressing cannabis use, particularly in vulnerable populations, is likely to have beneficial effects on psychiatric morbidity.

Keywords

cannabis, case–control, psychosis, psychotic symptoms, schizophrenia, systematic review

Introduction

Various lines of evidence suggest an association between cannabis and psychosis. These include case reports of cannabis use preceding onset of schizophrenia, psychosis in community surveys of cannabis users, and observational studies of psychosis in cannabis users (Bowes et al., 2001). The nature of this association is widely debated. Some authors contend that it may be due to socio-economic and demographic factors common to both substance use and schizophrenia (Phillips and Johnson, 2001; Phillips et al., 2002). Other studies suggest that there may be a shared aetiology for substance abuse and schizophrenia, such as common genetic factors (Tsuang et al., 1982) or dysregulation of neural circuitry mediating drug reward and reinforcement (Chambers et al., 2001). The self-medication hypothesis suggests that patients with schizophrenia use drugs to alleviate antipsychotic medication side-effects or aversive symptoms, such as negative symptoms of schizophrenia, anxiety, depression, or dysphoria (Hambrecht and Hafner, 2000). The vulnerability hypothesis postulates that the use of cannabis actually increases the risk of schizophrenia.

Support for this vulnerability hypothesis comes from a variety of sources. There is good evidence that cannabis intoxication may lead to brief psychotic episodes or recurrence of psychotic symptoms in individuals with a history of psychosis (Mathers and Ghodse, 1992). A challenge study using intravenous tetrahydrocannabinol (THC) in antipsychotic-treated patients with schizophrenia and controls found that THC exacerbated positive symptoms in patients and induced positive symptoms in controls, with a more
marked effect in patients (D’Souza et al., 2000). A review of neuroimaging studies of the effects of cannabinoids in humans found clear similarities between functional networks impaired by cannabis use and those known to be implicated in the pathogenesis of schizophrenia (Loeber and Yurgelun-Todd, 1999). Cannabinoid agonists have been shown to impair several aspects of cognition that are hallmark features of schizophrenia (Emrich et al., 1997). The finding of elevated endogenous cannabinoids (anandamide and palmitylethanolamide) in the cerebrospinal fluid of patients with schizophrenia, independent of gender, age or current medication (Leweke et al., 1999), raises the possibility that the endocannabinoid system may indeed have an aetiological role in schizophrenia. Indeed, there have now been two post-mortem studies demonstrating increased binding of [3H]CP-55940 (a synthetic cannabinoid-1 receptor agonist) in the dorsolateral prefrontal cortex (Brodmann’s area 9) of subjects with schizophrenia, independent of recent cannabis ingestion (Dean et al., 2001) and increased binding of [3H]SR141716A (a synthetic cannabinoid-1 receptor antagonist) in the anterior cingulate cortex of subjects with schizophrenia compared to controls (Zavitsanou et al., 2004).

The vulnerability hypothesis predicts that the risk of developing schizophrenia should be greater in those individuals who use cannabis compared to those who do not use cannabis. Five years ago, the only significant case–control study addressing this question was the widely discussed Swedish Conscription Cohort (Andreasson et al., 1987). Within the last few years, other studies have emerged, allowing the evidence for cannabis as a risk factor to be more systematically reviewed and assessed.

It is noteworthy that there have been a number of recent articles reviewing this topic (Arseneault et al., 2004; Smit et al., 2004) but no systematic reviews of the literature. Some of the published reports focus on the occurrence of psychotic symptoms, rather than operationally defined diagnostic criteria for schizophrenia or related psychoses. To clarify the epidemiological evidence for cannabis as a risk factor, we conducted a systematic review of all case–control studies, but only included in the meta-analysis those that clearly examined the association between cannabis use and schizophrenia or schizophrenia-like psychosis, not psychotic symptoms. Whereas other reviews have tended to discuss the literature more qualitatively (e.g., critiquing the methods used or the conclusions drawn from the data presented), we hoped to quantitatively examine all case–control studies to estimate the extent of heterogeneity between the studies, to assess whether there is any publication bias and to produce an estimate of the risk due to cannabis.

Methods

Data sources

Using established methods (Stroup et al., 2000), we sought observational studies examining the relationship between cannabis use and development of schizophrenia, reported between January 1966 and January 2004. We searched Embase, PsycINFO and Medline using the terms ‘cannabis’ and ‘schizophrenia’, as well as related search terms, including ‘psychosis’, both as free text and as expanded subject headings (full details of the search strategy are available on request). We retrieved additional references from reviews, selected articles and from a cited reference search (ISI-Web of Science). Reference lists of retrieved articles were also inspected for further potentially relevant studies.

Study selection

All articles containing original data on cannabis exposure and either schizophrenia or psychotic symptoms were reviewed. Case–control studies were included where exposure to cannabis preceded the onset of schizophrenia and where a diagnosis of schizophrenia or schizophrenia-like psychosis was confirmed using established criteria. The diagnosis could be made at face-to-face interview, by telephone using an interview schedule, or from existing health service data collected around the time of the illness. Cohort studies were included where healthy individuals were recruited at a time point before the median age of illness onset and where cannabis exposure was determined prospectively and blind to eventual diagnostic status. Studies where symptoms of psychosis were recorded, rather than a diagnosis of schizophrenia or schizophrenia-like psychosis, were also tabulated for further discussion, but were not included in the meta-analysis.

Data extraction

Studies were included in the meta-analysis where the initial numbers of people in the exposed and unexposed groups were reported, as well as the number who developed schizophrenia in each group, allowing reconstruction of two by two tables to determine the unadjusted odds ratios. Data were systematically extracted, and any ambiguous information was resolved through discussion between the three authors. A study was included only once if there were multiple publications by selecting the publication with the largest sample size. Unadjusted (crude) odds ratios were calculated and then combined using a fixed effects analysis. Crude rather than adjusted odds ratios were chosen because the method of adjustment differed across the included studies. Where evidence of heterogeneity was found (chi-squared heterogeneity, $p < 0.1$), a random effects analysis was applied. Summary odds ratios were reported using a Forest plot, and publication bias was examined by visual inspection of Begg’s funnel plot (Begg and Mazumdar, 1994) and using Egger’s test (Egger et al., 1997). All analyses were conducted using STATA 8 SE (STATA Corporation, College Station, TX, USA).

Results

The association between cannabis use and psychosis

Our search found 11 case–control studies examining the relationship between cannabis use and psychosis (Table 1). Although the methodological and statistical details of the studies and cannabis use psychosis criteria varied, there was nevertheless a surprising consistency in the unadjusted odds ratios (ORs) across all population groups studied. Nine
### Table 1  Case–control studies of psychosis (however defined) and cannabis use

<table>
<thead>
<tr>
<th>Study</th>
<th>Sample size (n)</th>
<th>Study design</th>
<th>Age range (years)</th>
<th>Unadjusted odds ratio: OR (95% CI)</th>
<th>Population studied</th>
<th>Cannabis use criteria</th>
<th>Psychosis criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Andreasson et al. (1987)</td>
<td>45570</td>
<td>Prospective (15-year follow-up)</td>
<td>Age at conscription: 18–21 years</td>
<td>2.41 (1.72–3.30)</td>
<td>Swedish conscripts (all male)</td>
<td>Structured interview for use of cannabis (number of reported occasions of use)</td>
<td>ICD-8 criteria for ‘schizophrenia’ (80% fulfilling DSM-III criteria)</td>
</tr>
<tr>
<td>Andreasson et al. (1989)</td>
<td>7695</td>
<td>Prospective (15-year follow-up)</td>
<td>Age at conscription: 18–21 years</td>
<td>2.06 (1.08–3.93)</td>
<td>Sub-population of conscripts from Stockholm County (all male)</td>
<td>Structured interview for use of cannabis (number of reported occasions of use)</td>
<td>ICD-8 criteria for ‘schizophrenia’</td>
</tr>
<tr>
<td>Rolfe et al. (1993)</td>
<td>420</td>
<td>Cross-sectional</td>
<td>'Cases': mean age 29.5 years</td>
<td>4.36 (2.65–7.15)</td>
<td>Gambian population (370 male, 50 female)</td>
<td>Positive urinary cannabinoid test</td>
<td>DSM-III criteria for schizophrenia</td>
</tr>
<tr>
<td>Grech et al. (1998)</td>
<td>225</td>
<td>Cross-sectional</td>
<td>'Cases': mean age 29.5 years</td>
<td>2.25 (1.22–4.14)</td>
<td>London-based population (sex ratio not stated)</td>
<td>'Cannabis use': criteria not stated</td>
<td>'Psychosis': criteria not stated</td>
</tr>
<tr>
<td>Grech et al. (1998)</td>
<td>107</td>
<td>Cross-sectional</td>
<td>'Cases': mean age 29.5 years</td>
<td>4.36 (0.44–43.33)</td>
<td>Maltese population (sex ratio not stated)</td>
<td>'Cannabis use': criteria not stated</td>
<td>'Psychosis': criteria not stated</td>
</tr>
<tr>
<td>Hall and Degenhardt (2000)</td>
<td>6722</td>
<td>Cross-sectional</td>
<td>Under 50 years</td>
<td>2.86 (1.37–5.99)</td>
<td>Australian National Survey of Mental Health and Well-Being (NSMHWB) (sex ratio not stated)</td>
<td>ICD-10 'Cannabis dependence'</td>
<td>Self-reported 'diagnosed with schizophrenia'</td>
</tr>
<tr>
<td>Arsenault et al. (2002)</td>
<td>759</td>
<td>Prospective</td>
<td>Assessed at age 11, 15, 18 and 26 years</td>
<td>3.71 (1.04–13.20)</td>
<td>New Zealand population: 'Dunedin birth cohort' (sex ratio not stated)</td>
<td>'Cannabis use' (3 times or more)</td>
<td>DSM-IV criteria for 'schizotypal disorder'</td>
</tr>
<tr>
<td>Farrell et al. (2002)</td>
<td>503</td>
<td>Cross-sectional</td>
<td>16–40+ years</td>
<td>3.27 (1.61–6.61)</td>
<td>UK prison population (394 male, 109 female)</td>
<td>Diagnostic Interview Schedule criteria for 'cannabis dependence' (daily use for 2 weeks or more)</td>
<td>ICD-10 criteria derived from the Schedules for Clinical Assessment in Neuropsychiatry (SCAN)</td>
</tr>
<tr>
<td>van Os et al. (2002)</td>
<td>4104</td>
<td>Cross-sectional</td>
<td>18–64 years</td>
<td>3.25 (1.48–7.15)</td>
<td>Netherlands population (sex ratio not stated)</td>
<td>'Cannabis use' derived from the Composite International Diagnostic Interview (CIDI)</td>
<td>DSM-III-R criteria using the Structured Clinical Interview (SCID)</td>
</tr>
<tr>
<td>Agostti et al. (2002)</td>
<td>5877</td>
<td>Cross-sectional</td>
<td>15–54 years</td>
<td>3.49 (1.35–9.02)</td>
<td>US National Comorbidity Survey (NCS): ‘noninstitutionalized’ population (sex ratio not stated)</td>
<td>DSM-III-R criteria for 'cannabis dependence' from modified CIDI</td>
<td>DSM-III-R criteria for 'nonaffective psychosis' from modified CIDI</td>
</tr>
<tr>
<td>Zammit et al. (2002)</td>
<td>41820</td>
<td>Prospective (26 year follow-up)</td>
<td>Age at conscription: 18–21 years</td>
<td>2.2 (1.7–2.8)</td>
<td>Swedish conscripts: follow-up of Andreasson’s 1987 study cohort (all male)</td>
<td>Structured interview for use of cannabis (number of reported occasions of use)</td>
<td>ICD-8/ICD-9 criteria for ‘schizophrenia’</td>
</tr>
</tbody>
</table>
studies provided sufficient data to conduct an odds ratio meta-
analysis (Figure 1). However, the Stockholm County Cohort
(Andreasson et al., 1989) was excluded on the grounds that it con-
tained data for a subpopulation of a previously reported study.
Similarly, the reanalysis of the Swedish Conscript Cohort (Zammit et al., 2002) was not included in the meta-analysis because, although the follow-up period was longer, the population size was smaller than the original study.

The random effects pooled OR was calculated for the remain-
ing seven studies (Andreasson et al., 1987; Rolfe et al., 1993;
Grech et al., 1998; Arsenault et al., 2002; Farrell et al., 2002;
van Os et al., 2002), with a derived value of 2.9 [95% confidence
interval (CI) = 2.3–3.6]. The fixed effects pooled OR was very
similar (OR = 2.9, 95% CI = 2.4–3.6). There was no evidence of
publication bias (Fig. 2) by visual inspection of Begg’s funnel plot
or using the Egger’s test (intercept = 0.78, t = 1.08, p = 0.33) and no
evidence of significant heterogeneity (chi-squared = 5.07, d.f. = 6,
p = 0.54). The unadjusted odds ratios of those studies excluded
were not substantively different from the pooled OR, with OR
values of 2.06 (Andreasson et al., 1989), 2.86 (Hall and
Degenhardt, 2000), 3.49 (Agosti et al., 2002) and 2.2 (Zammit et al., 2002). Of note, the Dunedin Birth Cohort Study (Arseneault et al., 2002) found that cannabis users by the age of 15 years had a higher OR for ‘schizophreniform disorder’ at age 26 years (OR = 4.50, 95% CI = 1.11–18.21) compared to those who started by age 18 years (OR = 1.65, 95% CI = 0.65–4.18). Even when the

Figure 1 Odds ratio meta-analysis plot (fixed effects). The Forest plot above shows the odds ratio from each study individually (squares) and the overall estimate from all studies combined (rhombus). The size of each square represents the weight given to that study in the meta-analysis. Studies supporting a positive association between cannabis and schizophrenia-like psychosis have estimates which lie to the right of the vertical line (odds ratio = 1, representing no effect in either direction). The width of the horizontal lines and rhombus represent the 95% confidence interval. Confidence intervals which do not cross the solid vertical line (of no effect) are also statistically significant.

Figure 2 (a) The log of the odds ratio to its standard error is plotted against the reciprocal of the standard error, such that the overall effect is represented as the gradient of the fitted line. Under the assumption of no publication bias, the intercept on the vertical axis should pass close to the origin. The graph shows that, although the line does not pass through the origin exactly, the confidence interval for the intercept (indicated by two small circles on the vertical axis) includes the origin. This may be interpreted as a lack of statistically significant publication bias. (b) A plot of study effect size (log odds ratio) against precision (SE of log odds ratio). In the absence of publication bias, the studies should spread out either side of the combined effect size estimate, indicated by a horizontal line in the above graph. Small studies to the right of the graph will spread out more from the horizontal line than large and more precise studies (to the left of the graph). Where studies with results in a certain direction are not published or identified, the spread of studies about the horizontal line will tend to be asymmetrical. The study effect sizes shown above are approximately symmetrical about the line of overall effect and the presence of publication bias is not supported.
The association between cannabis use and psychotic symptoms

A further six case–control studies were identified that rated psychotic symptoms in cannabis users compared to non-users (Tien and Anthony, 1990; Degenhardt et al., 2001; Degenhardt and Hall, 2001; Miller et al., 2001; Phillips et al., 2002; Fergusson et al., 2003) (Tables 2 and 3). These looked at both ‘high risk’ and ‘general’ populations.

One ‘high-risk’ study (Phillips et al., 2002) did not find an increased risk for the development of psychotic symptoms; however, the authors cautioned against ruling out cannabis as a risk factor for the development of psychosis because there was a low level of cannabis use in the sample studied and they did not monitor cannabis use after intake. A preliminary report of a study of a less heterogeneous population (people at high risk of developing schizophrenia for genetic reasons) did find cannabis to be an independent risk factor for the presence of psychotic symptoms, with a possible dose-related effect of both past and current cannabis use (Miller et al., 2001).

The largest cross-sectional study of a ‘general’ population (Degenhardt et al., 2001) also found a possible dose-related effect. Interestingly, a prospective longitudinal study of psychotic symptoms (Fergusson et al., 2003) found a higher rate ratio for psychotic symptoms at age 18 years than at age 21 years, suggesting that there may be greater vulnerability to the effects of cannabis in early adolescence. The Dunedin Birth Cohort Study (Arseneault et al., 2002) also found that, even when psychotic symptoms at age 11 years were controlled for, cannabis users by age 15 years and by age 18 years had significantly more ‘schizophrenia symptoms’ compared to controls (although data did not permit calculation of ORs).

Discussion

Despite considerable variation in how cannabis exposure and psychosis were elicited or defined, there is a notable consistency in unadjusted ORs across the population groups studied. The meta-analysis suggests that cannabis is a risk factor, increasing the chances of developing schizophrenia or a schizophrenia-like psychotic illness by approximately three-fold. This finding is supported by a
The dose–response relationship in the largest prospective study: the Swedish Conscript Cohort (Andreasson et al., 1987). The recent re-analysis of this cohort (Zammit et al., 2002) calculated adjusted ORs to allow for possible confounding factors, such as psychiatric diagnosis at conscription, IQ, and other socio-demographic factors. For subjects who had used only cannabis and no other drugs, this dose–response relationship remained significant, and the overall adjusted OR was 1.5 (95% CI = 1.1–2.0). For those who had used cannabis more than 50 times, the adjusted OR rose to 3.1 (95% CI = 1.7–5.5).

Further support for a ‘biological gradient’ is found in the studies of cannabis use and psychotic symptoms. Degenhardt and colleagues found an increase in the OR when DSM-IV criteria were used for cannabis dependence (OR 10.8) compared to cannabis abuse (OR 4.64) (Degenhardt and Hall, 2001; Degenhardt et al., 2001). In the Edinburgh ‘high risk’ population (Miller et al., 2001), the ORs for ‘past’ and ‘current’ cannabis use were 6.1 and 7.4, respectively, suggesting that the risk of significant psychotic symptoms is related both the pattern of cannabis use and schizophrenia vulnerability.

The vulnerability hypothesis for cannabis induced psychotic experiences was recently investigated using an experience sampling method to collect information on substance use and psychotic experiences in daily life (Verdoux et al., 2003). Verdoux et al. (2003) found that the acute effects of cannabis were modified by the subject’s level of vulnerability for psychosis, as defined by the Mini-International Neuropsychiatric Interview (MINI, 4.4 version) criteria (Amorin et al., 1998). Subjects with high vulnerability (who had experienced at least one bizarre psychotic symptom or at least two non-bizarre psychotic symptoms over the last month) were more likely to report perceived hostility, strange impressions or unusual perceptions than subjects with low vulnerability.

Table 3: Studies of ‘high-risk’ groups, cannabis use, and psychotic symptoms

<table>
<thead>
<tr>
<th>Study</th>
<th>Sample size (n)</th>
<th>Age range (years)</th>
<th>Unadjusted odds ratio (OR)</th>
<th>Population studied</th>
<th>Nature of ‘high risk’ status</th>
<th>Follow-up period</th>
<th>Cannabis use criteria</th>
<th>‘Psychosis’ criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Miller et al. (2001)</td>
<td>191</td>
<td>16–25 years</td>
<td>Current use:</td>
<td>Edinburgh High Risk Study: 155 ‘high risk’ subjects and 36 matched controls</td>
<td>No previous diagnosis of serious psychiatric disorder. At least 2 first- or second-degree relatives who suffered from schizophrenia</td>
<td>Present State Examination (PSE): evidence of delusions, hallucinations, or other behaviours, not sufficiently severe to meet the criteria for schizophrenic or related psychotic illness</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phillips et al. (2002)</td>
<td>100</td>
<td>14–28 years</td>
<td>1.43 (0.6–3.41) (non-significant)</td>
<td>Australian ‘ultra’ high risk cohort</td>
<td>3 groups (combined): ‘Trait and State Risk Factor Group’* ‘Attenuated Psychotic Symptoms Group’** ‘Brief Limited Intermittent Psychotic Symptoms Group’***</td>
<td>12 months</td>
<td>DSM-IV criteria for ‘cannabis dependence’ assessed using Schedules for Clinical Assessment in Neuropsychiatry (SCAN)</td>
<td>Present State Examination (PSE): evidence of delusions, hallucinations, or other behaviours, not sufficiently severe to meet the criteria for schizophrenic or related psychotic illness</td>
</tr>
</tbody>
</table>

*First-degree relative with a psychotic disorder or presence of schizotypal personality disorder and recent functional decline; **Presence of subthreshold psychotic symptoms; ***Episode(s) of frank psychosis lasting less than 1 week and spontaneously abated

Cannabis and psychosis
17 years have a lower percentage of cortical grey matter and an increased percentage white matter compared to those who start later, which is unrelated to duration of cannabis use (Wilson et al., 2000). It may be that adolescence to early adulthood is a period of time during which the developing brain is more vulnerable to the adverse effects of cannabis.

The question of whether cannabis is a precipitating or a causal factor in the development of schizophrenia remains. A recent study that used mathematical modelling to explore the possible effects of cannabis use and schizophrenia (Degenhardt et al., 2003) supported the possibility that cannabis precipitated psychosis in vulnerable individuals and that cannabis use is more likely among individuals with schizophrenia, but did not support a direct causal hypothesis. The main reason for this finding was the absence of any increase in the incidence of schizophrenia, despite clear increases in the use of cannabis in the Australian population studied. Any hypothesis that suggests that cannabis causes schizophrenia must explain this discrepancy in the epidemiological data. It may be that the cases caused by increased cannabis use have been offset by improvements in other risk factors (such as perinatal care) that might act to lower the incidence of schizophrenia. Alternatively, it could be that, for cannabis to exert such a direct causative effect, it is necessary for an individual to have been exposed during adolescence. Some authors argue that this pattern of cannabis use is a fairly recent phenomenon, emerging only in the 1990s, and that rates of schizophrenia in the general population are likely to increase over the next 10 years (Arseneault et al., 2003). There may already be some evidence for this in areas of London (Boydell et al., 2003).

Recent attempts to explain the association between drug misuse and schizophrenia have utilized the vulnerability hypothesis (Tsapakis et al., 2003), placing it within the framework of current ideas regarding the neurobiology of psychosis (Kapur, 2003). Doubts have been raised about the self-medication hypothesis (Smit et al., 2003) in view of cannabis remaining a risk factor for schizophrenia even when premorbid psychotic symptoms are controlled for. This has strengthened the view that some individuals with schizophrenia might be biologically vulnerable to the rewarding effects of drugs of abuse (Potvin et al., 2003). In general terms, this may relate to dysregulation of neural circuitry mediating drug reward, reinforcement and saliency. Cannabis use during adolescence or early adult life may be one of a number of environmental stressors that interact with genetic factors to predispose an individual to later psychotic illness. Predisposed individuals may also be particularly sensitive to the psychotomimetic effects of cannabis. In this model, cannabis use is neither necessary nor sufficient to cause psychotic illness, but it may act as a risk factor for both vulnerability and time to onset of psychotic illness. This latter prediction is borne out by a study investigating first episode psychosis in the Netherlands, which found that cannabis users presented earlier than non-users, with a median age difference of 7.5 years (95% CI = 4.7–10.4 years) (Veen et al., 2004). Patterns of drug misuse, particularly cannabis, may help to explain the finding of an earlier age of onset of schizophrenia being observed in male compared to female patients in the published literature from the last two decades (Aleman et al., 2003). Given that early onset is also associated with a poorer prognosis for schizophrenia, addressing this issue may have important outcome implications for those who are at high risk of developing schizophrenia for genetic reasons.

Our findings underline the need to recognize the use of cannabis as a significant risk factor for schizophrenia and schizophrenia-like psychotic illness. Further research is necessary, particularly if we are to understand the role played by the endocannabinoid system in the aetiology of schizophrenia. Whatever these aetiological implications, clinicians and those involved in planning health policy have a responsibility to positively encourage any interventions likely to reduce the use of cannabis, particularly in vulnerable populations, because these are likely to have significant beneficial effects on psychiatric morbidity.

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