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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 (Bowers *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

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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 [^{3}H]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 [^{3}H]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 Conscript 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 methodologies 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

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

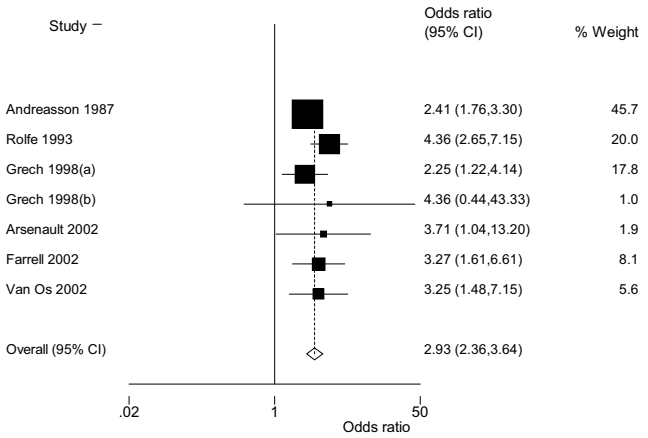

Figure 1 Odds ratio meta-analysis plot (fixed effects). The Forest plot above shows the odds ratio from each study individually (squares) and the overall estimate from all studies combined (rhombus). The size of each square represents the weight given to that study in the meta-analysis. Studies supporting 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

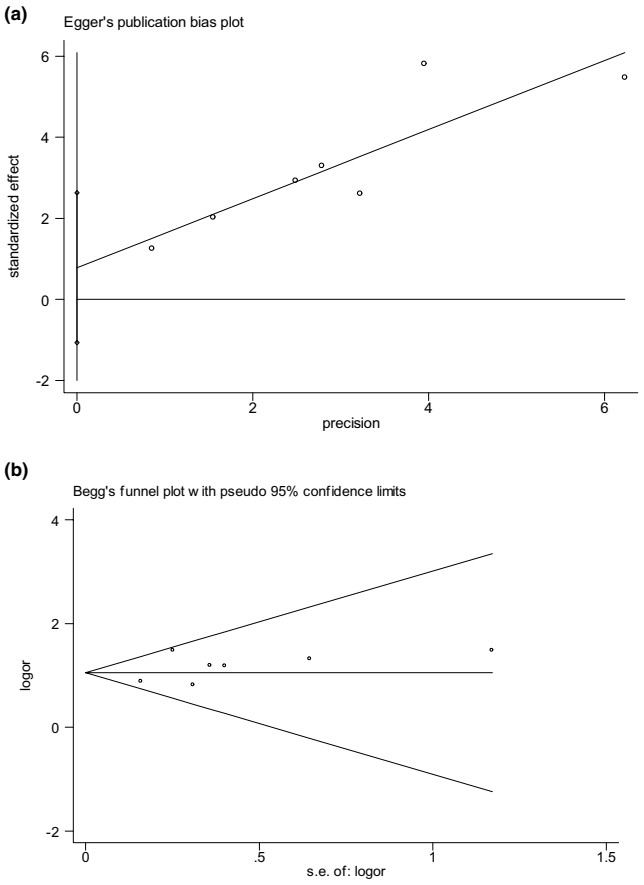

Figure 2 (a) The log of the odds ratio to its standard error is plotted against the reciprocal of the standard error, such that the overall effect is represented as the gradient of the fitted line. Under the assumption of no publication bias, the intercept on the vertical axis should pass close to the 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

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 contained 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 remaining seven studies (Andreasson *et al*., 1987; Rolfe *et al*., 1993; Grech *et al*., 1998; Arseneault *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 presence of psychotic symptoms, before cannabis use, at age 11 years, was accounted for, the OR remained high (OR = 3.12, 95% CI = 0.73–13.29), suggesting that early cannabis use may confer greater risk for psychosis outcomes.

Table 2 Case–control studies of reported psychotic symptoms and cannabis use

Study	Sample size (*n*)	Age range (years)	Unadjusted odds ratio (OR)	Population studied	Cannabis use criteria	Criteria for psychotic symptoms
Tien and Anthony (1990)	4994	18–49 years	2.62	US National Institute of Mental Heath (NIMH) Epidemiological Catchment Area Program: household survey	Self-reported daily use of cannabis	'Self-reported psychotic experiences' (1 or more positive responses from 12 items of the Diagnostic Interview Schedule (DIS) relating to delusions and hallucinations)
Degenhardt *et al.* (2001)	10641	18–35+ years	3.56 (use) 4.64 (abuse) 10.80 (dependence)	Australian National Survey of Mental Health and Well-Being (NSMHWB)	'No use': less than 6 occasions in last year 'Use': more frequent, but not meeting DSM-IV criteria DSM-IV criteria for 'cannabis abuse' DSM-IV criteria for 'cannabis dependence'	Score of 3 or more on 'psychosis screener' comprising 7 items: delusions of control, thought interference and passivity, delusions of reference and persecution, and grandiose delusions
Degenhardt and Hall (2001)	6722	Under 50 years	3.98 (use) 4.15 (weekly use) 5.86 (disorder)	Subset of NSMHWB dataset	'Cannabis use': undefined 'Weekly cannabis use' 'Cannabis use disorder': meeting any DSM-IV 'disorder' criteria	Score of 3 or more on 'psychosis screener' comprising 7 items: delusions of control, thought interference and passivity, delusions of reference and persecution, and grandiose delusions
Fergusson *et al.* (2003)	1025 (age 18 years) 1011 (age 21 years)	Data gathered at age 18 and 21 years	'Rate ratio' for mean psychotic symptoms: 3.7 (age 18 years) 2.3 (age 21 years) 1.8 (adjusted for confounds, including previous symptoms)	New Zealand birth cohort: the Christchurch Health and Development Study (CHDS)	DSM-IV criteria for 'cannabis dependence' derived from the Composite International Diagnostic Interview (CIDI)	Total number of 'psychotic symptoms' in past month using 10 items from the Symptom Checklist 90 (SCL-90)

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

Table 3 Studies of 'high-risk' groups, cannabis use, and psychotic symptoms

Study	Sample size (*n*)	Age range (years)	Unadjusted odds ratio (OR)	Population studied	Nature of 'high risk' status	Follow-up period	Cannabis use criteria	'Psychosis' criteria
Miller *et al.* (2001)	191	16–25 years	Current use: *Occasional*: 1.3 (0.5–3.1) *Frequent*: 7.4 (2.4–22.6) Past use: *Occasional*: 1.0 (0.5–2.2) *Frequent*: 6.1 (2.1–17.6)	Edinburgh High Risk Study: 155 'high risk' subjects and 36 matched controls	No previous diagnosis of serious psychiatric disorder. At least 2 first- or second-degree relatives who suffered from schizophrenia	Data for 'at entry' psychotic symptoms only	Structured interview for 'cannabis use' past and current: none, occasional, frequent	Present State Examination (PSE): evidence of delusions, hallucinations, or other behaviours, not sufficiently severe to meet the criteria for schizophrenic or related psychotic illness
Phillips *et al.* (2002)	100	14–28 years	1.43 (0.6–3.41) (non-significant)	Australian 'ultra' high risk cohort	3 groups (combined): 'Trait and State Risk Factor Group'* 'Attenuated Psychotic Symptoms Group'** 'Brief Limited Intermittent Psychotic Symptoms Group'***	12 months	DSM-IV criteria for 'cannabis dependence' assessed using Schedules for clinical assessment in neuropsychiatry (SCAN)	BPRS: a least one significant score for hallucinations, delusions, paranoia, or formal thought disorder; held with strong conviction (3+ on CASH); daily frequency; lasting longer than 1 week

*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

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.

Just as the genetic risk of schizophrenia and psychosis proneness (previous experience of psychotic symptoms) may define populations that are particularly vulnerable to the effects of cannabis, it may also be the case that early exposure to cannabis may increase the risk of developing psychiatric problems. The possibility of a vulnerable age group was raised by the findings of both Arseneault *et al*. (2002) and Fergusson *et al*. (2003) for schizophreniform disorder and psychotic symptoms, respectively. A recent brain imaging study has interestingly found evidence that both males and females who start using cannabis before the age of

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 causative 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*., 2004). 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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