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ORIGINAL ARTICLE

Cannabis, schizophrenia and other non-affective psychoses: 35 years of follow-up of a population-based cohort

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Background. There is now strong evidence that cannabis use increases the risk of psychoses including schizophrenia, but the relationship between cannabis and different psychotic disorders, as well as the mechanisms, are poorly known. We aimed to assess types of psychotic outcomes after use of cannabis in adolescence and variation in risk over time.

Method. A cohort of 50 087 military conscripts with data on cannabis use in late adolescence was followed up during 35 years with regard to in-patient care for psychotic diagnoses.

Results. Odds ratios for psychotic outcomes among frequent cannabis users compared with non-users were 3.7 [95% confidence interval (CI) 2.3–5.8] for schizophrenia, 2.2 (95% CI 1.0–4.7) for brief psychosis and 2.0 (95% CI 0.8–4.7) for other non-affective psychoses. Risk of schizophrenia declined over the decades in moderate users but much less so in frequent users. The presence of a brief psychosis did not increase risk of later schizophrenia more in cannabis users compared with non-users.

Conclusions. Our results confirm an increased risk of schizophrenia in a long-term perspective, although the risk declined over time in moderate users.

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Key words: Cannabis, psychosis, schizophrenia.

Introduction

While the evidence on the association between cannabis and schizophrenia is very robust (Moore *et al*. 2007; Hall & Degenhardt, 2009), there are still unresolved issues regarding the nature of the association and the causal direction. In a recent review, the precise nature of the association between cannabis use and the development of schizophrenia was highlighted as the first among several unanswered questions regarding the health effects of cannabis (Winstock *et al*. 2010).

Several studies from recent years have given support for a causal association between cannabis and psychosis, including schizophrenia (van Os *et al*. 2002; Zammit *et al*. 2002; Henquet *et al*. 2008), and there is also evidence that cannabis alters the course and prognosis of schizophrenia (Zammit *et al*. 2008; Foti *et al*. 2010). Although there are biologically plausible mechanisms for the association related to the dopamine system (Murray *et al*. 2007), the mechanisms are not clear (Henquet *et al*. 2008). It has been suggested that the link between cannabis and psychotic development is stronger during adolescence than during adulthood (Arseneault *et al*. 2002; Konings *et al*. 2008), though not all studies have found this (Moore *et al*. 2007). Better knowledge on how cannabis use in adolescence influences long-term psychiatric outcomes would be valuable in understanding the role of cannabis in the development of schizophrenia and other psychotic outcomes.

Another clinically important issue is whether cannabis-related psychotic disorder is a risk factor for schizophrenia. Arendt *et al*. (2005) followed 535 cases of cannabis-induced psychotic symptoms and found that 44.5% of these cases later developed a schizophrenia-spectrum disorder. However, an episode of brief psychosis is common before a diagnosis

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of schizophrenia is established. Castagnini & Berrios (2009), in a review of the literature, found that around half of the cases of acute and transient psychotic disorders [International Classification of Diseases, 10th revision (ICD-10) F23] convert mainly into either schizophrenia or affective disorders. Thus it would be of interest to find out whether an episode of brief or transient psychosis is a precursor of schizophrenia to a greater extent in cannabis-exposed subjects than in non-users. In the above-mentioned study by Arendt *et al*. (2005), there was no information on risk of schizophrenia among cases with other (non-cannabis-related) types of brief psychosis. It could also be the case that other factors associated with cannabis use could confound the association between cannabis-induced psychosis and subsequent schizophrenia.

As several authors have pointed out (Johns, 2001; Hall & Degenhardt, 2004), the diagnosis 'cannabis-induced psychosis' is controversial, and Thornicroft suggested as far back as 1990 that clinicians discontinue the term 'cannabis psychosis' (Thornicroft, 1990) and instead use other appropriate diagnoses according to the ICD, 9th revision (ICD-9) at the time. Thus it may be appropriate to follow up a larger spectrum of brief psychotic conditions with the aim to find out whether a brief psychosis in the presence of cannabis abuse increases the risk of subsequent schizophrenia compared with other cases of brief psychosis.

In order to address these issues, we have performed an additional follow-up of the cohort of Swedish conscripts, previously used to assess the association between cannabis and schizophrenia (Andréasson *et al*. 1987; Zammit *et al*. 2002). While it is still the only population-based cohort with enough power to assess schizophrenia as a specific outcome (Moore *et al*. 2007), we are also able to assess the effect of cannabis on other types of psychotic outcomes.

The aims of the study were to: (1) assess the risk of schizophrenia, brief psychosis and other non-affective psychoses among cannabis users compared with non-users; (2) examine to what extent the increased risk of schizophrenia and other psychotic outcomes varies over time up to the age of 55 years; and (3) examine whether the occurrence of brief psychotic episodes among cannabis users increases the risk of schizophrenia to a greater extent than episodes among non-users.

Method

Study population

The cohort consisted of 50 087 Swedish men who were conscripted during 1 year (1969–1970) for compulsory military training. Over 93% of the men were aged 18–19 years. Only 2–3% of men were exempted from conscription mainly because of a severe mental or physical handicap or a congenital disorder. All of the men completed two non-anonymous, self-report questionnaires at the time of conscription. The first questionnaire concerned social background, upbringing conditions, friendship, relationships, attitudes, and adjustment at school and work. The second questionnaire concerned the use of alcohol, tobacco and information about substance use.

All conscripts were assessed by a psychologist after a structured interview and psychological test as well as an IQ test. Those presenting with psychiatric symptoms were referred to a psychiatrist and subjects with psychiatric disease were diagnosed according to the ICD-8 (eighth revision). Permission to use the database for research purposes was granted by the Research Ethics Committee of the Karolinska Institute and the Swedish Data Inspection Board.

Exposure

Information on cannabis and other drugs was obtained from the questionnaire on use of alcohol, tobacco and substance use. Questions were asked whether subjects had ever used drugs, which drugs had ever been used, first drug used, drug most commonly used, frequency of use and questions regarding use of specific drugs from a list with alternatives.

Level of cannabis use was categorized as frequency of use as follows: never; once; 2–4; 5–10; 11–50; >50. In some analyses, due to small numbers of cases, we collapsed all those who reported cannabis use in a group 'ever used cannabis'.

Confounders

As found in previous research and in earlier studies in this population (Zammit *et al*. 2002), psychiatric diagnosis at conscription, IQ score, 'disturbed behaviour', having been brought up in a city and cigarette smoking are associated with schizophrenia (David *et al*. 1997; Malmberg *et al*. 1998) and are also likely to be related to cannabis use. These variables were thus included as confounders in the analysis. Disturbed behaviour is a composite score variable obtained from the self-reported questionnaire regarding experiences from earlier in life of truancy, contact with the police or child-care authorities and running away from home (Zammit *et al*. 2002). IQ score was classified into a normalized standard nine-point scale.

Outcomes

Schizophrenia

The Swedish national hospital discharge register, which contains all in-patient admissions for psychiatric care in Sweden, was used to record all psychiatric admissions from 1970 until 2007. Diagnoses were coded according to the Swedish versions of ICD: ICD-8 during 1965–1986; ICD-9 during 1987–1996; and ICD-10 during 1997–2007. The diagnosis code of schizophrenia was 295 according to ICD-8 and ICD-9 and F20 according to ICD-10.

Brief psychosis

Brief psychosis was analysed as an outcome in itself and also to assess whether the occurrence of brief psychotic episodes among cannabis users increases the risk of schizophrenia compared with non-users. We included the following diagnostic categories in this group:

Psychosis associated with drugs or poison intoxication: 294.30 psychosis associated with other physical conditions/drug or poison intoxication (ICD-8); 292 drug psychosis (ICD-9); F125 and F127 psychotic disorder due to use of cannabinoids (ICD-10).
Reactive psychosis: 298 reactive psychosis (ICD-8 and ICD-9).
Transient psychotic disorders: 293 transient organic psychotic conditions (ICD-9); F23 acute and transient psychotic disorders (ICD-10).

Other non-affective psychoses

The following diagnoses were included in 'other non-affective psychoses':

Unspecified non-organic psychosis: 299.99 psychoses NUD (ICD-8); F28 other non-organic psychotic disorders and F29 unspecified non-organic psychosis (ICD-10).
Paranoid psychosis: 297 paranoia (ICD-8 and ICD-9); F22 persistent delusional disorders (ICD-10).

Analysis

Of all 50 087 conscripts, 8144 (16.3%) subjects had missing information in the variables included in the model, including 3381 (6.8%) participants who did not respond to the question on drug use. Thus, 41 943 subjects were included in the final analysis. Logistic regression was used to calculate odds ratios and 95% confidence intervals (CIs) for developing schizophrenia, brief psychosis and other non-affective psychoses among cannabis users, and to assess the risk of schizophrenia and brief psychosis by decades, from 1973 until 2007. Analysis by using Cox regression made no difference, thus we retained logistic regression as the method of analysis. We report both crude results and results adjusted for confounders as above. We estimated the incidence of schizophrenia among individuals with a brief psychotic disorder and compared this in those with or without a history of cannabis use. Linear hypothesis testing was performed to calculate p value for trend to test for a dose–response association. The analyses were performed in SAS 9.1 for Windows (SAS Institute Inc., USA).

Results

A total of 322 (0.8%) cases of schizophrenia, 149 (0.4%) of brief psychosis and 126 (0.3%) for other non-affective psychoses occurred among all 41 943 subjects during the 35 years of follow-up. About 10% reported ever use of cannabis.

Table 1 shows odds ratios for schizophrenia and other psychotic outcomes by three main categories of cannabis use. Subjects reporting cannabis use had increased odds ratios for all psychotic outcomes. After adjustment for confounders, these associations persisted for schizophrenia and psychosis associated with drugs. The very high odds ratio for psychosis associated with drugs (21.8, 95% CI 8.3–57.0) among those with the highest consumption level was considerably reduced after adjustment (7.8, 95% CI 2.1–27.7).

Table 2 shows the main categories of psychotic outcomes by level of reported cannabis use. A dose-dependent association was found between frequency of cannabis use and risk of schizophrenia (p for trend <0.01). The dose–response association was weaker for brief psychosis and other non-affective psychoses, although the p value for trend was significant for brief psychosis. Subjects with the highest level of cannabis use had an approximately four-fold increase in odds of schizophrenia, and two-fold increased odds for brief psychosis and other non-affective psychoses compared with non-users.

As shown in Table 3, there was a decline in the odds ratios of schizophrenia across the decades among subjects who reported ever use of cannabis but much less so in those who reported the highest level of use. The odds ratios for brief psychosis did not decline over the decades but appeared to actually increase over time, particularly among those with highest use, although this was based on a small number of cases and CIs were wide.

Out of the 160 cases of brief psychosis among non-cannabis users, 41 (26%) later got a diagnosis of schizophrenia. Among the 39 cases of brief psychosis

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Table 1. *Association between cannabis use and schizophrenia and other non-affective psychoses*

	No. of exposed	No. of cases	Crude OR (95% CI)	Adjusted[a] OR (95% CI)
Schizophrenia				
Never used cannabis	37 328	255	1	1
Ever used cannabis[b]	4615	67	2.1 (1.6–2.8)	1.8 (1.3–2.5)
>50 times	767	32	6.3 (4.3–9.2)	3.7 (2.3–5.8)
Brief psychosis				
Psychosis associated with drugs or poison intoxication[c]				
Never used cannabis	37 073	14	1	1
Ever used cannabis[b]	4548	11	6.4 (2.9–14.1)	3.2 (1.3–8.0)
>50 times	735	6	21.8 (8.3–57.0)	7.8 (2.1–27.7)
Reactive psychosis[d]				
Never used cannabis	37 073	73	1	1
Ever used cannabis[b]	4548	12	1.3 (0.8–2.4)	1.2 (0.6–2.2)
>50 times	735	5	3.5 (1.4–8.6)	2.5 (0.9–6.7)
Transient psychotic disorders[e]				
Never used cannabis	37 073	41	1	1
Ever used cannabis[b]	4548	11	2.1 (1.1–4.1)	1.7 (0.8–3.7)
>50 times	735	2	2.4 (0.5–9.9)	1.0 (0.2–5.2)
Other psychoses				
Unspecified non-organic psychosis[f]				
Never used cannabis	37 073	58	1	1
Ever used cannabis[b]	4548	13	1.8 (1.0–3.3)	1.5 (0.7–3.0)
>50 times	735	4	3.4 (1.2–9.6)	2.3 (0.7–7.1)
Paranoid psychosis[g]				
Never used cannabis	37 073	56	1	1
Ever used cannabis[b]	4548	11	1.6 (0.9–3.0)	1.6 (0.8–3.4)
>50 times	735	3	2.7 (0.8–8.6)	2.6 (0.7–9.5)

OR, Odds ratio; CI, confidence interval; ICD-8, International Classification of Diseases, 8th revision; ICD-9, ICD, 9th revision; ICD-10, ICD, 10th revision.

[a] Psychiatric diagnosis at conscription, IQ score, disturbed behaviour, smoking, brought up in a city.

[b] The category 'ever used cannabis' comprises all who reported cannabis use, including those who reported '>50 times'.

[c] 294.30 Psychosis associated with other physical conditions/drug or poison intoxication (ICD-8); 292 drug psychosis (ICD-9); F125 and F127 psychotic disorder due to use of cannabinoids (ICD-10).

[d] 298 Reactive psychosis (ICD-8 and ICD-9).

[e] 293 Transient organic psychotic conditions (ICD-9); F23 acute and transient psychotic disorders (ICD-10).

[f] 299.99 Psychoses NUD (ICD-8); F28 other non-organic psychotic disorders and F29 unspecified non-organic psychosis (ICD-10).

[g] 297 Paranoia (ICD-8 and ICD-9); F22 persistent delusional disorders (ICD-10).

in subjects who had ever used cannabis, nine (23%) subjects developed schizophrenia (Table 4). Thus, the incidence of schizophrenia was virtually the same among cases of brief psychosis with cannabis history compared with those without. We also assessed whether the risk of schizophrenia among cannabis users was increased among those with a diagnosis of brief psychosis, but his was not the case (data not shown).

Discussion

Our study confirms the strong association between cannabis and psychotic disorders, with a more than three-fold increased risk for schizophrenia, and two-fold increased risk for other psychotic outcomes in those using cannabis most frequently. For schizophrenia, we observed a dose–response association, as in previous studies (Zammit *et al*. 2002), but for the other types of psychosis evidence for a dose–response effect was weaker. The associations were stronger in the highest consumption category, consistent with previous studies (McGrath *et al*. 2010; Kuepper *et al*. 2011), in which only subjects with the longest duration of cannabis use had a significantly increased risk of psychosis.

It does seem as if the association between cannabis and schizophrenia may be stronger than that between

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Table 2. *ORs for psychotic outcomes by reported frequency of cannabis use*

	Schizophrenia				Brief psychosis				Other non-affective psychoses			
Cannabis use	No. of exposed	No. of cases	Crude OR (95% CI)	Adjusted[a] OR (95% CI)	No. of exposed	No. of cases	Crude OR (95% CI)	Adjusted[a] OR (95% CI)	No. of exposed	No. of cases	Crude OR (95% CI)	Adjusted[a] OR (95% CI)
Never	37 328	255	1	1	37 073	119	1	1	37 073	104	1	1
Once	1044	4	0.5 (0.2–1.4)	0.6 (0.3–1.8)	1040	4	1.2 (0.4–3.2)	1.1 (0.4–3.0)	1040	5	1.6 (0.6–4.1)	1.8 (0.7–4.7)
2–4 times	1363	12	1.3 (0.7–2.3)	1.3 (0.7–2.4)	1351	6	1.2 (0.5–2.8)	1.2 (0.5–3.1)	1351	2	0.5 (0.1–2.1)	0.4 (0.1–2.0)
5–10 times	796	8	1.4 (0.7–2.9)	1.3 (0.6–2.6)	788	3	1.2 (0.4–3.7)	0.9 (0.3–2.9)	788	3	1.3 (0.4–4.2)	1.1 (0.3–3.7)
11–50 times	645	11	2.5 (1.3–4.5)	1.9 (1.0–3.6)	634	7	3.4 (1.5–7.3)	2.5 (1.1–5.5)	634	5	2.7 (1.1–6.8)	1.8 (0.7–4.9)
> 50 times	767	32	6.3 (4.3–9.2)	3.7 (2.3–5.8)	735	10	4.2 (2.2–8.2)	2.2 (1.0–4.7)	735	7	3.3 (1.5–7.2)	2.0 (0.8–4.7)
Total	41 943	322			41 621	149			41 621	126		
p value for trend			< 0.01				< 0.01				0.09	

OR, Odds ratio; CI, confidence interval.

[a] Diagnosis of psychiatric illness on conscription, disturbed behaviour, low IQ score, brought up in a city, cigarette smoking.

cannabis and other non-affective psychoses. Even in the higher consumption categories, we observed only weak evidence for an increase in odds of brief psychoses after adjusting for confounders. Other studies have not been able to assess the effect of cannabis specifically on schizophrenia, but have examined a broader range of schizophrenia-spectrum disorders (Moore *et al*. 2007). Our finding of a stronger association regarding schizophrenia is consistent with the 'cannabis–psychosis persistence model' recently presented by Kuepper *et al*. (2011), in which cannabis particularly would have an effect on persistent types of psychoses, such as schizophrenia, and in a dose–response fashion.

We observed a decline in the risk of schizophrenia associated with cannabis across the decades. Of the cases related to cannabis use, 60% occurred during the first decade compared with 45% among non-users of cannabis. This result is consistent with the theory that cannabis use can trigger an earlier onset of the disease (Arseneault *et al*. 2002; Smit *et al*. 2004; Konings *et al*. 2008). The decline across the decades may also suggest a decrease in the consumption of cannabis and a weaker effect as the interval between exposure and outcome increases. While lacking longitudinal data from Sweden, Chen & Kandel (1995) showed a steady decline in marijuana use from the ages of 20–25 years in the USA, and there are similar findings from European countries (Nahas & Latour, 1993).

The fact that those with the highest exposure remain with a higher risk throughout the follow-up period may indicate that they also continue cannabis use for a longer period. While we have consumption data only from the time of conscription, Solowij & Grenyer (2002) summarized studies showing that about 10% of those who ever use cannabis and one-third to one-half of those who use daily will become dependent on cannabis and use it despite experiencing problems.

We did not find evidence that the occurrence of schizophrenia among patients with brief psychosis was higher in those with a cannabis history compared with those without. Arendt *et al*. (2005) found that that nearly 50% of people diagnosed with cannabis-induced psychotic symptoms later developed a schizophrenia-spectrum disorder. Castagnini & Berrios (2009) found that around 50% of cases with acute and transient psychotic disorders subsequently meet criteria for either schizophrenia or affective psychoses. Thus, the finding by Arendt *et al*. (2005) might just reflect the fact that this is the proportion of persons with any type of brief psychosis who develop schizophrenia.

Thus, while brief psychotic episodes are a common precursor of schizophrenia (around 25% in our study, around 50% in others), there is little evidence that

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Table 3. *Adjusted ORs for psychotic outcomes by decade of first admission for psychotic disorder*

	Total population, *n*	1970–1979		1980–1989		1990–1999		2000–2007	
		Cases, *n*	Adjusted[a] OR (95% CI)	Cases, *n*	Adjusted[a] OR (95% CI)	Cases, *n*	Adjusted[a] OR (95% CI)	Cases, *n*	Adjusted[a] OR (95% CI)
Schizophrenia									
Never used cannabis	37 328	117	1	76	1	46	1	16	1
Ever used cannabis[b]	4615	40	2.2 (1.4–3.3)	17	1.9 (1.1–3.5)	7	1.2 (0.5–2.8)	3	0.7 (0.2–3.0)
>50 times	767	18	4.1 (2.2–7.6)	8	3.9 (1.6–9.4)	3	2.5 (0.7–9.0)	3	2.7 (0.5–14.0)
Brief-psychosis									
Never used cannabis	37 073	18	1	46	1	42	1	13	1
Ever used cannabis[b]	4548	5	1.8 (0.6–5.6)	8	1.0 (0.4–2.3)	11	1.5 (0.7–3.1)	6	3.9 (1.3–11.8)
>50 times	735	1	1.2 (0.1–10.0)	5	3.4 (1.1–10.9)	4	2.1 (0.6–7.1)	–	–

OR, Odds ratio; CI, confidence interval.

[a] Diagnosis of psychiatric illness on conscription, disturbed behaviour, low IQ score, brought up in a city, cigarette smoking.

[b] The category 'ever used cannabis' comprises all who reported cannabis use, including those who reported '>50 times'.

Table 4. *Occurrence of schizophrenia among patients treated for brief psychosis*

	Total population, *n*	No. of cases with brief psychosis[a]	No. of cases with schizophrenia	Crude OR (95% CI)	Adjusted[b] OR (95% CI)
Never used cannabis	37 328	160	41	1	1
Ever used cannabis[c]	4615	39	9	0.8 (0.3–1.9)	1.1 (0.4–3.1)
>50 times	767	14	4	1.1 (0.3–3.8)	1.2 (0.2–5.9)

OR, Odds ratio; CI, confidence interval; ICD-8, International Classification of Diseases, 8th revision; ICD-9, ICD, 9th revision; ICD-10, ICD, 10th revision.

[a] 294.30 Psychosis associated with other physical conditions/drug or poison intoxication (ICD-8); 292 drug psychosis (ICD-9); F125 and F127 psychotic disorder due to use of cannabinoids (ICD-10); 298 reactive psychosis (ICD-8 and ICD-9); 293 transient organic psychotic conditions; F23 acute and transient psychotic disorders (ICD-10).

[b] Diagnosis of psychiatric illness on conscription, disturbed behaviour, low IQ score, brought up in a city, cigarette smoking.

[c] The category 'ever used cannabis' comprises all who reported cannabis use, including those who reported '>50 times'.

those with a cannabis-induced psychotic disorder have a greater risk of transition from brief psychotic episodes to schizophrenia compared with those who do not use cannabis. Again, referring to the model suggested by Kuepper *et al*. (2011), cannabis use is moderately associated with brief psychotic episodes and strongly associated with persistent psychosis, but cannabis does not seem to play a major role in the transition from brief psychotic episodes to schizophrenia.

As far as we know, this is the largest study to date that has examined the relationship between cannabis and psychotic disorders, including schizophrenia. Several methodological issues need to be taken into consideration. First, we are limited in that we have only data regarding use of cannabis before conscription. If drug use persisted or declined after conscription, our findings probably underestimate the effect of cannabis on psychotic disorders. Second, only males were included in this study. The incidence of schizophrenia can vary across decades between men and women and it is suggested that the gender difference is modulated by age, so it would be valuable to assess the association also in women. Third, identification of diagnoses of schizophrenia and other psychosis was limited to in-patient care, so our findings may not be applicable to milder forms of schizophrenia not requiring in-patient care. Fourth, the validity of self-reports on cannabis use can be questioned. Since this was part of assessment for military training, it is possible that conscripts would under-report since drug use indicates deviant behaviour, but also that they might over-report in order to be exempted from the compulsory military training. The

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prevalence of cannabis use in the age group is, however, consistent with school surveys and other surveys carried out in Sweden around that time (Nahas & Latour, 1993). In general, the level of use has been lower than in several other European countries and the USA (Nahas & Latour, 1993; MacCoun & Reuter, 1997; Hickman *et al*. 2007). Any misreporting is unlikely to be related to later incidence of psychotic conditions.

In spite of these limitations, this study strengthens previous findings of association between cannabis use and psychotic disorders, and clarifies issues relating to variability in risk over time, and the relationship between cannabis use, brief psychosis and subsequent onset of schizophrenia.

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Declaration of Interest

None.

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