# Self reported cannabis use as a risk factor for schizophrenia in Swedish conscripts of 1969: historical cohort study

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## Abstract

**Objectives** An association between use of cannabis in adolescence and subsequent risk of schizophrenia was previously reported in a follow up of Swedish conscripts. Arguments were raised that this association may be due to use of drugs other than cannabis and that personality traits may have confounded results. We performed a further analysis of this cohort to address these uncertainties while extending the follow up period to identify additional cases.
**Design** Historical cohort study.
**Setting** 1969-70 survey of Swedish conscripts (>97% of the country's male population aged 18-20).
**Participants** 50 087 subjects: data were available on self reported use of cannabis and other drugs, and on several social and psychological characteristics.
**Main outcome measures** Admissions to hospital for ICD-8/9 schizophrenia and other psychoses, as determined by record linkage.
**Results** Cannabis was associated with an increased risk of developing schizophrenia in a dose dependent fashion both for subjects who had ever used cannabis (adjusted odds ratio for linear trend of increasing frequency 1.2, 95% confidence interval 1.1 to 1.4, $P<0.001$), and for subjects who had used only cannabis and no other drugs (adjusted odds ratio for linear trend 1.3, 1.1 to 1.5, $P<0.015$). The adjusted odds ratio for using cannabis >50 times was 6.7 (2.1 to 21.7) in the cannabis only group. Similar results were obtained when analysis was restricted to subjects developing schizophrenia after five years after conscription, to exclude prodromal cases.
**Conclusions** Cannabis use is associated with an increased risk of developing schizophrenia, consistent with a causal relation. This association is not explained by use of other psychoactive drugs or personality traits relating to social integration.


## Introduction

The relation between cannabis use and subsequent onset of psychosis is complex.[1–3] An association between self reported use of cannabis in adolescence and subsequent risk of schizophrenia was reported from a cohort study of Swedish conscripts,[4] which supports the view that cannabis might act as an independent risk factor for schizophrenia. Several uncertainties have, however, been raised regarding the interpretation of this result.

Firstly, the apparent effect of cannabis may be caused by other drugs (such as amphetamines).[5 6] Secondly, premorbid personality traits may have predisposed individuals both to developing schizophrenia and to using cannabis. Thirdly, use of cannabis may have been secondary to the presence of schizophrenia, as a form of "self medication" for symptoms, despite failure to identify the disorder at the time of conscription.[7] Review of case histories of a small subsample from this cohort shows that the association was not due to use of other drugs and that use of cannabis preceded any mental illness,[8] but the causal pathways are difficult to disentangle.

In this study we perform a further analysis of the Swedish conscript cohort to address some of these concerns.[4] The follow up period is now 27 years (15 years in the original study) and covers almost the whole period of risk for schizophrenia.[9] Our improved understanding of risk factors for schizophrenia has also enabled us better to adjust for factors such as personality traits that potentially confound this relation.[10–13]

## Methods

### Subjects

The cohort consisted of 50 087 Swedish men conscripted for compulsory military training in 1969-1970. More than 98% (49 321) were 18-20 years of age. Only 2-3% of the male population were excused conscription because of severe mental or physical handicap. The conscription procedure included intelligence tests and non-anonymous self reported questionnaires on family, social background, behaviour during adolescence, and substance use—including first drug used, drug most commonly used, frequency of use, and direct questions regarding use of a list of specified drugs. Details of the procedure and results of studies of its validity have been reported previously.[14]

All subjects reporting any psychiatric symptoms were interviewed by a psychiatrist and given a diagnosis where applicable.[15] Thirty four cases of psychosis diagnosed at conscription were excluded from the study.

### Follow up

Sweden's national hospital discharge register recorded about 70% of all psychiatric admissions in 1970 and has been virtually complete since 1987. The linkage reported here was from 1970 to 1996. The incomplete registration is unlikely to have affected the results. Misclassification of outcomes is likely to be low, given that over 90% of people with schizophrenia are admitted to hospital at some point during their illness.[16]

Patients were given clinical diagnoses according to the Nordic version of ICD-8 (ICD-9 from 1987). Outcomes investigated were schizophrenia and other psychoses. Satisfactory validity of schizophrenia diagnoses in a small sample from this cohort has been observed.[8]

### Analysis

We used logistic regression to calculate odds ratios and 95% confidence intervals for developing schizophrenia in subjects who used cannabis compared with subjects with no history of drug use, both before and after adjustment for potential confounders.

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**Table 1** Crude and adjusted odds ratios with 95% confidence intervals for developing schizophrenia any time after conscription in subjects who have ever used cannabis

| Drug use | No of subjects | No (%) of subjects developing schizophrenia | Odds ratio (95% CI) | |
|---|---|---|---|---|
| | | | Crude | Adjusted* |
| Cannabis ever† | 5391 | 73 (1.4) | 2.2 (1.7 to 2.8) | 1.5 (1.1 to 2.0) |
| Frequency of use of cannabis (ever): | | | | |
| None | 36 429 | 215 (0.6) | 1.0† | 1.0† |
| Once | 608 | 2 (0.3) | 0.6 (0.1 to 2.2) | 0.6 (0.1 to 2.3) |
| 2-4 times | 1380 | 8 (0.6) | 1.0 (0.5 to 2.0) | 0.9 (0.4 to 1.9) |
| 5-10 times | 806 | 9 (1.1) | 1.9 (1.0 to 3.7) | 1.4 (0.7 to 2.8) |
| 11-50 times | 689 | 13 (1.9) | 3.2 (1.8 to 5.7) | 2.2 (1.2 to 4.0) |
| >50 times | 731 | 28 (3.8) | 6.7 (4.5 to 10.0) | 3.1 (1.7 to 5.5) |
| Linear trend for frequency of use | — | — | 1.4 (1.3 to 1.5) | 1.2 (1.1 to 1.4) |

*Adjusted for diagnosis at conscription to IQ score to poor social integration to disturbed behaviour to cigarette smoking to and place of upbringing.
†No drug use as baseline comparison.

Eleven different variables were considered to be potential confounders and included in the analysis (see bmj.com). The variable relating to poor social integration as an aspect of personality was a summed score of questions regarding number of close friends, history of relationships with girlfriends, and individual sensitivity. Only 3% of the sample had missing data for any of the questions.

Subjects were stratified into those receiving a diagnosis within five years of conscription (0-5 years) and those receiving a diagnosis after this time (>5 years) to investigate possible effects of a prodrome at the time of conscription.

## Results

Out of the 50 053 subjects, 362 (0.71%, 95% confidence interval 0.65% to 0.80%) received a diagnosis of schizophrenia by 1996. Data on drug use, derived from all sources of information, were missing on 16 (4.4%) of subjects developing schizophrenia and on 1522 (3.1%) of non-cases ($P<0.2$).

Of the 11 variables initially included as potential confounders, only five had any effect on the adjusted results. Adjusting for poor social integration made minimal difference to results (see bmj.com).

### Ever used cannabis

Altogether 5391 subjects (10.8% of the cohort) had ever used cannabis, and 73 of these (1.4%) developed schizophrenia. In 69 subjects who started using drugs before 1969, 19 (31%; 95% confidence interval 20% to 44%) of those developing schizophrenia had stopped using drugs before conscription, as opposed to 2810 (64%; 62% to 65%) of the 4418 who did not develop schizophrenia ($P<0.001$).

The crude odds ratio for developing schizophrenia any time after conscription was 2.2 (1.7 to 2.8) and this association persisted, although reduced, after adjustment (table 1).

We found a dose dependent relation between frequency of cannabis use and risk of schizophrenia. The largest risk was seen in subjects reporting use of cannabis on more than 50 occasions.

The association between cannabis use and schizophrenia was greater in subjects admitted in the first five years after conscription (adjusted odds ratio 2.1, 1.2 to 3.7) compared with those admitted after five years (1.2, 0.8 to 1.8). Frequency of cannabis use was associated with schizophrenia in both the early onset group (adjusted odds ratio for linear trend 1.3, 1.1 to 1.6, $P<0.001$) and the later onset group (1.2, 1.1 to 1.3, $P<0.02$) (see bmj.com).

### Cannabis only

Altogether 1648 subjects (3.3% of cohort, 3.1% to 3.5%) had used only cannabis, and 18 of these (1.1%, 0.6 to 1.7%) developed schizophrenia. Those who used only cannabis had an increased risk of schizophrenia compared with those who reported no drug use. The odds ratios before and after adjustment were similar (table 2). We also found a dose dependent relation for frequency of use.

### Stimulant use

We found an association between schizophrenia and stimulant use in the crude analysis (crude odds ratio 3.8, 2.7 to 5.4), but this became non-significant after adjustment for confounders (adjusted odds ratio 1.5, 0.9 to 2.4). Adjusting for frequency of cannabis use further reduced the association between stimulant use and risk of schizophrenia (adjusted odds ratio 1.1, 0.6 to 2.1). The association observed between schizophrenia and frequency of cannabis use was unchanged after adjustment for stimulant use.

### Other psychoses

A total of 446 subjects were admitted with other psychoses. Subjects who had ever used cannabis had an increased risk of developing a psychosis other than schizophrenia (crude odds ratio 1.4, 1.1 to 1.9), but this effect was reduced after adjustment (adjusted odds ratio 1.1, 0.8 to 1.5). A similar pattern was observed for the association with cannabis frequency, with a linear trend odds ratio of 1.1 (1.0 to 1.2, $P<0.02$) before

**Table 2** Adjusted odds ratios with 95% confidence intervals for developing schizophrenia any time after conscription for subjects taking cannabis only

| Drug use | No of subjects | No (%) of subjects developing schizophrenia | Odds ratio (95% CI) | |
|---|---|---|---|---|
| | | | Crude | Adjusted* |
| Cannabis ever† | 1 635 | 18 (1.1) | 1.9 (1.2 to 3.0) | 1.9 (1.1 to 3.1) |
| Frequency of use of cannabis (ever): | | | | |
| None | 36 429 | 215 (0.6) | 1.0† | 1.0† |
| Once | 245 | 0 | — | — |
| 2-4 times | 499 | 5 (1.0) | 1.7 (0.7 to 4.2) | 1.9 (0.8 to 4.8) |
| 5-10 times | 255 | 3 (1.2) | 2.0 (0.6 to 6.3) | 1.7 (0.5 to 5.7) |
| 11-50 times | 176 | 1 (0.6) | 1.0 (0.1 to 6.9) | 0.8 (0.1 to 6.0) |
| >50 times | 70 | 4 (5.7) | 10.2 (3.7 to 28.3) | 6.7 (2.1 to 21.7) |
| Linear trend for frequency of use | — | — | 1.3 (1.1 to 1.6) | 1.3 (1.0 to 1.5) |

*Adjusted for diagnosis at conscription, IQ score, poor social integration, disturbed behaviour, cigarette smoking, and place of upbringing.
†No drug use as baseline comparison.

adjustment and of 1.0 (0.9 to 1.1, $P < 0.85$) after adjustment.

For all the analyses, diagnosis on conscription, IQ score, and place of upbringing contributed most to confounding. Adjusting for the other potential confounders made virtually no difference to the final adjusted results.

## Discussion

The association between use of cannabis and schizophrenia was stronger in subjects who were first admitted within five years of conscription. Subjects with a prodrome of schizophrenia at conscription may have increased their cannabis use, perhaps as a means of self medication.[2] But all subjects were screened at conscription, and we adjusted for other psychiatric problems recorded at that time. The relation with cannabis use was also observed in subjects admitted more than five years after conscription. It seems more likely that the reduced association in the group with later onset is due to misclassification, as the number of people who discontinued cannabis use accumulated over time.[17]

Although adjustment for confounders substantially reduced the odds ratios, adjusting for poor social integration had only minimal effects. Personality traits are difficult to measure accurately, however, and residual confounding remains a possibility. The association between cannabis and schizophrenia persisted even after adjusting for use of alcohol, cigarettes, and other drugs. This implies that a shared risk factor (be it biological, genetic, or through personality traits) for developing schizophrenia and for using psychoactive substances does not adequately explain the association observed.

We are limited in that we have only data regarding use of cannabis before conscription. But if the pattern of increased initiation and reduced cessation of drug use seen in the schizophrenia group persisted after the time of conscription, this would result in us underestimating the effect size of cannabis. Any effect of underreporting of cannabis use would again result in an underestimate of the true effect size. Non-response was similar for subjects developing schizophrenia and non-cases.

We did not find an independent association between use of stimulants and schizophrenia, although power was reduced compared with other analyses.

There is accumulating evidence that cannabis has detrimental effects on mental health in some people.[3] Molecular studies have shown that $\Delta^9$-tetrahydrocannabinol, the active component of cannabis, increases release of dopamine in the mesolimbic pathway.[18] Given the suggested relation between increased mesolimbic dopamine and positive symptoms of schizophrenia,[19] such observations provide support for the hypothesis that cannabis may act as a risk factor for this disorder.

Use of cannabis has increased in the United Kingdom, and 50% of the population now report having used cannabis at least once.[20] If cannabis increases the risk of schizophrenia by 30%, as implied by these results, then 13% of cases of schizophrenia could be prevented if cannabis use was eliminated from the population. The overall weight of evidence is that occasional use of cannabis has few harmful effects overall.[2] Nevertheless, these results indicate a potentially serious risk to the mental health of people who use cannabis, particularly in the presence of other risk factors for schizophrenia. Such risks need to be considered in the current move to liberalise and possibly legalise the use of cannabis in the United Kingdom and other countries.

### What is already known about this topic

Use of cannabis has been associated with an increased risk of developing schizophrenia

Alternative explanations for this association include confounding by personality or by use of other drugs such as amphetamines, and use of cannabis as a form of self medication secondary to the disorder

### What this study adds

Self reported cannabis use is associated with an increased risk of subsequently developing schizophrenia, consistent with a causal relation

This association is not explained by sociability personality traits, or by use of amphetamines or other drugs

Self medication with cannabis is an unlikely explanation for the association observed

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