Cannabis use predicts future psychotic symptoms, and vice versa

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ABSTRACT

Aims To assess if cannabis use is a risk factor for future psychotic symptoms, and vice versa, in adolescents and young adults from the general population.
Design Cohort study.
Setting/participants 'Zuid Holland' study, a 14-year follow-up study of 1580 initially 4–16-year-olds who were drawn randomly from the Dutch general population. Because cannabis use is generally condoned in the Netherlands, false-negative reports of cannabis use may occur less frequently than in countries with stricter drug policies, which supports the value of the present study.
Measurements Life-time cannabis use and psychotic symptoms, assessed with the Composite International Diagnostic Interview (CIDI).
Findings Cannabis use, in individuals who did not have psychotic symptoms before they began using cannabis, predicted future psychotic symptoms (hazard ratio = 2.81; 95% confidence interval = 1.79–4.43). However, psychotic symptoms in those who had never used cannabis before the onset of psychotic symptoms also predicted future cannabis use (hazard ratio = 1.70; 95% confidence interval = 1.13–2.57).
Conclusions The results imply either a common vulnerability with varying order of onset or a bi-directional causal relationship between cannabis use and psychosis. More research on patterns and timings of these relationships is needed to narrow down the possibilities.

KEYWORDS Adolescents, cannabis, CIDI, psychosis.

INTRODUCTION

Although the association between cannabis use and psychosis has been documented for clinical samples (Ziedonis & Trudeau 1997; Fowler *et al.* 1998), general population samples (Regier *et al.* 1990; Kessler *et al.* 1997; Degenhardt & Hall 2001) and samples of incarcerated individuals (Farrell *et al.* 2002; Vreugdenhil *et al.* 2003), studies aimed at unravelling the direction of the causal chain are rare. It has been suggested that individuals who suffer from psychosis begin to use cannabis to self-medicate their symptoms (Noordsy *et al.* 1991; Hambrecht & Hafner 1996), whereas others argue that exposure to cannabis increases the risk of psychosis (Arseneault *et al.* 2002; Van Os *et al.* 2002; Arseneault *et al.* 2004). If, indeed, cannabis use not only constitutes a consequence of, but also acts as a risk factor for the emergence of psychosis, this might have consequences for preventative efforts.

Only a few studies investigated the hypothesis that cannabis use precipitates psychosis, or represents a risk factor in psychosis-naive individuals (Andreasson *et al.* 1987; Arseneault *et al.* 2002; Van Os *et al.* 2002; Zammit *et al.* 2002; Degenhardt *et al.* 2003; Verdoux *et al.* 2003; Henquet *et al.* 2005). Arseneault *et al.* (2002) conducted a follow-up of 759 individuals from a New Zealand birth cohort. They found that, after correction for possible confounding effects of psychotic symptoms at age 11, and

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use of other substances, self-reported cannabis use ('three times or more') by age 15 and by age 18 predicted later schizophrenia symptoms. Cannabis use by age 15 was a stronger predictor than cannabis use by age 18. However, because they did not ascertain whether, between age 11 and ages 15 or 18, psychotic symptoms had developed, the onset of psychotic symptoms may still have preceded the onset of cannabis use.

Van Os *et al.* (2002) conducted a 3-year follow-up of 4045 psychosis-free subjects and 59 individuals who fulfilled criteria for psychotic disorder, aged 18–64 years, from the Dutch general population. They found that baseline cannabis use predicted the future presence of psychotic symptoms. However, the risk difference in the presence of a psychosis diagnosis at follow-up was only 2.2% in the initially psychosis-free subjects, versus 54.7% in those with a diagnosis of psychotic disorder at initial assessment. Hence, in the absence of a diagnosis of psychotic disorder, cannabis use seemed to constitute a minor risk factor for psychosis. This was confirmed by Henquet *et al.* (2005), who studied 2437 German adolescents (average age 18.3 years) from a population-based sample, who were followed-up across an interval of 3.5 years. The studies by Van Os *et al.* (2002) and Henquet *et al.* (2005) both did not concern younger adolescents. The New Zealand study (Arseneault *et al.* 2002) indicated that early onset (before age 15) of cannabis use might be a stronger risk factor for psychosis than cannabis use in later adolescence. Hence, in an early-onset group, cannabis use may constitute a stronger risk factor for psychosis than reported by Van Os *et al.* (2002) or Henquet *et al.* (2005).

Further evidence for the role of cannabis use as a risk factor for psychosis was provided by Zammit *et al.* (2002). These authors assessed cannabis use in 50 087 Swedish conscripts aged 18–20 years in 1970. They followed them across the period from 1970 to 1996, and found that the risk for schizophrenia was increased (odds ratio = 1.9) in those who reported that they had ever used cannabis at initial assessment. The effect was dose-dependent. For those who had used cannabis more than 50 times prior to initial assessment, the odds ratio for schizophrenia was 6.7. The diagnosis of schizophrenia was based on data from the Swedish national hospital discharge register.

Verdoux *et al.* (2003) assessed 79 individuals with high or low levels of cannabis use from a sample of 685 French university students (mean age = 22.1 years). They obtained day-by-day information regarding cannabis use and psychotic symptoms in daily life. They also assessed psychosis with a standardized psychiatric interview (Mini-International Neuropsychiatric Interview; MINI; Sheehan *et al.* 1998). Subjects were significantly more likely to experience unusual perceptions in the periods marked by cannabis use. The effects of cannabis were restricted to the 3 hours surrounding its consumption.

In contrast, Degenhardt *et al.* (2003) assessed eight Australian birth cohorts (1940–44, 1945–49, 1950–54, 1955–59, 1960–64, 1965–69, 1970–74, 1975–79), and did not find evidence for an increase in the prevalence of schizophrenia in the general population, parallel to an increased prevalence of cannabis use. Schizophrenia prevalence data were obtained from psychiatric case registers, which implies that several biases, such as referral biases or differences in the way schizophrenia was defined across time, may have influenced the results.

Although previous studies provided some evidence for the role of cannabis as a risk factor for psychotic symptoms, psychosis may also constitute a risk factor for cannabis use. Individuals with incipient psychosis might use substances to self-medicate their symptoms (Noordsy *et al.* 1991; Hambrecht & Hafner 1996). Hambrecht & Hafner (1996), for instance, investigated 232 first-episode schizophrenia patients and found that the first symptom of schizophrenia was more often followed than preceded by use of illicit drugs. Cannabis use was by far the most frequently used drug. Hence, this cross-sectional study indicates that psychotic symptoms may place individuals at risk for cannabis use. To our knowledge, there have been no longitudinal general population studies that examined whether psychotic symptoms in adolescents acted as a risk factor for future cannabis use. The single study that covered adolescence examined only whether cannabis use was a risk factor for psychosis (Arseneault *et al.* 2002). To disentangle the association between psychotic symptoms and cannabis use, studies that investigate both possible temporal directions, from cannabis use to psychosis and vice versa, are needed. If temporal directions would run in both ways, this might even suggest that common aetiological factors are responsible for both psychotic symptoms and cannabis use.

In the present study, two hypotheses were tested: (1) cannabis use is a risk factor for psychotic symptoms and (2) psychotic symptoms constitute a risk factor for cannabis use. Four- to 16-year-olds who were drawn randomly from the Dutch general population were followed-up across a 14-year period. Data regarding onset of cannabis use and psychotic symptoms were used to test both hypotheses. Because cannabis use is generally condoned in the Netherlands, false-negative reports of cannabis use may occur less frequently than in countries with stricter drug policies.

METHODS

Sample

The original target population consisted of children and adolescents 4–16 years of age, from the Dutch province

of Zuid-Holland. In 1983 (time 1), a random sample of 2600 of these children and adolescents (100 children of each sex and each birth year cohort) was drawn from municipal registers that list all residents in this province. Two small municipalities of a total of 86 declined to participate. These two municipalities contained 78 individuals of the sample that was drawn from the municipal registers. Hence, 2522 children and adolescents remained. Of the 2447 parents who were reached, 2076 (84.4%) cooperated (Verhulst *et al.* 1985a; 1985b). This sample was followed-up until 1997, when the sixth assessment took place (time 6). Of the 2076 individuals who were assessed at time 1, 1016 were male and 1060 female. More details on the initial data collection are presented elsewhere (Verhulst *et al.* 1985a; 1985b).

In 1997, data regarding life-time cannabis use and life-time psychotic symptoms were obtained with the Composite International Diagnostic Interview (CIDI; World Health Organization 1993) from 1580 (732 males, 848 females) of the 2076 individuals for whom time 1 data were available. Corrected for deceased ($n = 8$), mentally retarded ($n = 12$) and emigrated ($n = 59$) subjects, the response rate was 79%. The other 417 subjects who had not been interviewed with the CIDI ('dropouts') were compared to those who remained in the study ($n = 1580$) to investigate selective dropout. These two groups did not differ with respect to time 1 Child Behaviour Checklist (CBCL; Achenbach 1991) Total problems scores ($t = 1.04$, $P = $ NS), scores on the time 1 CBCL thought problems scale, that might indicate psychotic symptoms ($t = 1.21$, $P = $ NS), and scores on the time 1 CBCL items 'sees things that aren't there' ($t = -0.44$, $P = $ NS) and 'uses alcohol or drugs' ($t = -0.21$, $P = $ NS). Dropouts had somewhat lower scores on time 1 CBCL item 'hears things that aren't there' ($t = 2.23$, $P < 0.05$; mean item score 0.01 versus 0.03). Furthermore, boys tended to drop out more often than girls ($\chi^2 = 18.0$, $P < 0.001$). Dropouts were 284 males and 212 females. From these analyses it can be concluded that, with regard to the level of psychopathology, those who were interviewed at time 6 were generally similar to those who dropped out, and do not seem to have constituted a less problematic subsample. More details were reported earlier (Hofstra *et al.* 2000).

Instruments

The CIDI (World Health Organization 1997) is a structured respondent-based interview that can be used to assess *Diagnostic and Statistical Manual* version IV (DSM-IV) Axis I disorders. Good reliability and validity of the CIDI have been reported (Andrews & Peters 1998). For the present study, data based on the CIDI sections regarding psychosis and cannabis use were analysed. The psychosis section contains 23 questions regarding psychotic symptoms. If at least one of the symptoms has ever been present, the earliest age at onset is asked. The CIDI question regarding cannabis use 'Have you ever used cannabis more than five times to get high, to relax, to feel better, more active or more alert?' was used to assess life-time cannabis use. In case of a positive answer, age of first use is asked.

Statistical analyses

Cox regression analyses (Cox 1972) were conducted with SAS version 8.2 statistical software. In the first set of analyses, it was determined whether cannabis use was a risk factor for psychotic symptoms. Survival time was defined in years, as age at onset of psychotic symptoms or, if psychotic symptoms did not occur, as the age at the final assessment, at time 6. Because survival time was only known in years, we used the exact method in SAS for the treatment of ties. If more than one psychotic symptom was reported present, with different ages at onset, the earliest age at onset was used in the analyses. Hazard ratios (HR) were computed that indicate the association between cannabis use and future psychotic symptoms. Because onset of cannabis use occurred during the course of the study, and not at a fixed age for all cannabis users, cannabis use was entered as a time-dependent covariate (Singer & Willett 1991). The time-dependent covariate was defined as $X(t) = 1$ if the individual had started using cannabis, until the age of t-1, and $X(t) = 0$ if else. As the age range at time 1 was considerable (12 years), possible cohort effects were adjusted for by fitting stratified Cox regressions, in which age groups at time 1 were used as strata. Sex was entered in the analyses in a similar way, so we adjusted for the possible effects of sex. Furthermore, the proportional hazards assumption was tested for the time-dependent covariate by testing its interaction with time (age).

It is possible that retrospective reports of age of onset of cannabis use or psychotic symptoms are not reliable enough, although this has been contradicted by previous research (Wittchen et al. 1989; Johnson & Mott 2001; Parra et al. 2003). In any case, to minimize effects of recall bias all regression analyses were repeated, prerequiring a minimum interval of 2 years between onset of cannabis use and onset of psychotic symptoms. All individuals who provided age of onset data for cannabis use and psychotic symptoms that fell within the same 2-year range were excluded from these analyses. Only data from individuals who reported that psychotic symptoms took place at least 2 years after onset of cannabis use were analysed. In this way, a putative influence of recall bias on the results of the study was minimized.

Similar sets of survival analyses were conducted to test whether psychosis is a risk factor for cannabis use.

Ethics

Each assessment phase of this study was approved by the Committee for Medical Ethics, Sophia Children's Hospital/Erasmus Medical Center Rotterdam. At each phase, written informed consent was obtained from all subjects who completed a questionnaire (parents and youths), after the procedure had been fully explained.

RESULTS

Associations between life-time psychotic symptoms and life-time cannabis use are presented in Table 1. A significant association was found ($\chi^2 = 22.9$, $P < 0.001$), although the strength of the association was small ($\kappa = 0.11$, $P < 0.001$). The mean age of onset of cannabis use was 16.6 years. Cannabis use occurred before the onset of psychotic symptoms in 32 individuals. In these individuals, the average interval between cannabis use and psychotic symptoms was 4.6 years. The mean age of onset of psychotic symptoms was 17.2 years. Psychotic symptoms preceded cannabis use in 25 individuals. In these individuals, the average interval between psychotic symptoms and cannabis use was 7.8 years. In six individuals, onset of cannabis use and psychotic symptoms occurred at the same age.

Prediction of psychotic symptoms

Cannabis use predicted psychotic symptoms. The hazard ratio of 2.81 (95% CI = 1.79–4.43) indicates that the risk of future psychotic symptoms in those who used cannabis was increased almost threefold. With the requirement of a minimum period of 2 years between cannabis use and the onset of psychotic symptoms, the hazard ratio remained significant (2.07; 95% CI = 1.20–3.57). The interaction between cannabis use and time was not significant.

Table 1 Frequencies of life-time cannabis use and psychotic symptoms.

	Cannabis use		
Psychotic symptoms	*Absent (n)*	*Present (n)*	*Total*
Absent (*n*)	1110	305	1415
Present (*n*)	102	63	165
Total	1212	368	1580

Prediction of cannabis use

Psychotic symptoms predicted cannabis use. The hazard ratio was 1.70 (95% CI = 1.13–2.57), and remained significant (1.79; 95% CI = 1.13–2.83) when only those in whom cannabis use started at least 2 years later than psychotic symptoms were analysed. The interaction between psychotic symptoms and time was not significant.

DISCUSSION

The relationship between cannabis use and psychotic symptoms was examined in a 14-year follow-up study of a random sample of initially 4–16-year-olds from the Dutch general population. Life-time cannabis use (and its age of onset) and life-time psychotic symptoms (and the time of their onset) were assessed retrospectively at the end of the 14-year follow-up period, when subjects were 18–30 years old.

Our first hypothesis was confirmed: cannabis use was a risk factor for psychotic symptoms in initially psychosis-free individuals. Furthermore, significant associations between cannabis use and future psychosis were found, despite the low age at study end-point in some individuals, the youngest being only 18 years old at time 6. Because psychosis usually develops after the age of 18 (Salokangas *et al.* 2003), many individuals who might have displayed psychotic symptoms at further follow-up may have been rated free of psychotic symptoms. This may have diminished effect sizes in the present study. However, it can also be argued that cannabis is not a risk factor for psychosis, but only decreases the age of onset (Veen *et al.* 2004). If true, such an effect may have inflated our results.

It is possible, but unlikely, that recall bias has influenced the results. Re-analyses conducted to assess if temporal associations were present over a minimal time-span of 2 years yielded similar results as the initial analyses. The number of individuals used for these re-analyses was smaller than the number used for the initial analyses, given the fact that individuals who reported onset of cannabis use and psychotic symptoms within a 2-year period were excluded. However, despite the longer interval and the smaller power, due to the smaller number of subjects, the re-analyses yielded similar results as the initial analyses. Results by Parra *et al.* (2003) also indicate that it is unlikely that the results have been affected by recall bias. These authors found that, across an 11-year longitudinal study in adolescents and young adults, the overall mean-level change in reported age of onset of illicit drug use between year 1 and year 11 of the study was only 0.32 years, whereas the intraclass correlation between

ages of onset, assessed at different assessment waves, was 0.69. Similar results were reported by Johnson & Mott (2001), who also reported that, of all drugs, questions regarding first use of cannabis were the most reliable. Furthermore, Wittchen *et al.* (1989) reported about the high accuracy of retrospective reports of age at onset of psychotic symptoms, assessed with the CIDI. Recall bias may also indicate that individuals, erroneously, do not remember at all having used cannabis or having experienced psychotic symptoms in the past, instead of just reporting the wrong age at onset. It seems to us that the risk of this type of recall bias is higher for psychotic symptoms than for cannabis use. We do not know if such recall bias has been present. If it has, it has resulted in a decrease in the associations between cannabis use and psychotic symptoms in the present study.

The findings of the present study corroborated results of previous studies that indicated that cannabis use is a risk factor for future psychotic symptoms (Arseneault *et al.* 2002; Van Os *et al.* 2002; Zammit *et al.* 2002), whereas results by others (Degenhardt *et al.* 2003; Verdoux *et al.* 2003) were contradicted. Verdoux *et al.* (2003) used a selected sample of university students, who may be less vulnerable for psychotic symptoms, for instance, given the negative association between psychotic features and IQ (Zammit *et al.* 2004) or socioeconomic status (Aro *et al.* 1995). Furthermore, Verdoux *et al.* (2003) assessed short-term effects, whereas the study by Van Os *et al.* (2002) indicated that life-time cannabis use was a stronger predictor of psychosis than recent cannabis use. The study by Degenhardt *et al.* (2003), as stated in the introduction, was limited by unstandardized assessment and possible referral biases.

The second hypothesis, that psychotic symptoms are a risk factor for future cannabis use in the absence of a life-time history of cannabis use, was also confirmed. The finding that psychotic symptoms predicted cannabis use may be considered as supportive for the self-medication hypothesis (Hambrecht & Hafner 1996).

It is remarkable that, in the present study, links between psychotic features and cannabis seemed to run in both directions, from cannabis use towards psychotic symptoms, and vice versa. This might indicate that a common type of vulnerability factor is responsible for the association found. In some who are vulnerable cannabis use might precede psychosis, and in others the reverse might occur. For instance, increased density of cannabinoid receptors has been associated with cannabis use, as well as with schizophrenia (Dean *et al.* 2001). If such common vulnerabilities existed at the receptor level, individuals with psychotic symptoms, due to such neuroanatomical properties, would be more vulnerable for effects of cannabis than psychosis-free individuals. Indeed, it has been shown (Van Os *et al.* 2002) that effects of cannabis use on the risk of future psychotic disorder are much larger in those adults from the general population who had already displayed psychotic symptoms at initial assessment, compared to initially psychosis-free individuals.

It is also possible that mechanisms responsible for the cannabis—psychosis pathway differ from those that are responsible for the psychosis—cannabis pathway. For instance, cannabis might be a toxic agent that renders individuals vulnerable for psychosis, which might account for the cannabis—psychosis pathway, but not vice versa. Long-lasting effects of cannabis use might be associated with an increased density of cannabinoid receptors in the caudate-putamen (Dean *et al.* 2001). Van Os *et al.* (2002) hypothesized that this increased density might result in increased vulnerability for psychosis, given the close interaction between cannabinoid receptors and dopaminergic receptors, the latter being thought to play a role in the pathogenesis of psychotic symptoms.

The study may have been limited by the retrospective nature of the information regarding onset of cannabis use and psychotic symptoms. However, analyses that required an interval of 2 years or more between the first report of cannabis use and the onset of psychotic symptoms did not reveal different results, which renders effects of recall bias less likely. Another limitation of the study is the validity of the information regarding psychotic symptoms obtained with the CIDI. Respondents' answers regarding the presence of psychotic symptoms were taken at face value, instead of being checked by a clinician. It might also be argued that psychotic symptoms in the general population do not necessarily relate to clinically significant psychotic disorder. However, the usefulness of studying psychotic symptoms instead of using diagnostic criteria for psychotic disorder was demonstrated by previous studies (Van Os *et al.* 2000; Johns & Van Os 2001) that found that psychosis, like other psychiatric conditions such as anxiety or depression, may exist as a continuous phenotype in the population. In other words, while only a few individuals from the general population fulfill DSM criteria for psychotic disorder, many may display psychotic features that may be considered as weaker expressions of a similar phenotype as full-blown psychotic disorders.

The findings may have implications for public health policies. Psychosis-free adolescents who begin to use cannabis seem to constitute a vulnerable group. Our findings suggest that cannabis use should be discouraged by parents, teachers, and health workers. Prevention of cannabis use might lower the risk for future psychotic symptoms. However, it may be the case that cannabis use and psychotic symptoms share a common underlying vulnerability. If this were the case, prevention of cannabis use might not affect the risk for future psychotic

symptoms. Future studies that assess effects of prevention of cannabis use on the incidence of psychotic symptoms are warranted.

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