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Early exposure to cannabis and risk for psychosis in young adolescents in Trinidad

Konings M, Henquet C, Maharajh HD, Hutchinson G, Van Os J. Early exposure to cannabis and risk for psychosis in young adolescents in Trinidad.

Objective: Cannabis use increases the risk for psychosis, but psychotogenic effects of cannabis may be restricted to exposure during early adolescence.
Method: Four hundred and seventy-two participants (aged 12–23 years), randomly selected from the general population in Trinidad, completed questionnaires on past and current cannabis use and psychotic symptoms (using the Community Assessment of Psychic Experiences).
Results: Cannabis use increased the risk of experiencing psychotic symptoms and this effect was conditional on early exposure, defined around the mean age of onset of cannabis use. Thus, exposure before but not after the age of 14 years predicted psychotic symptoms (respectively β: 0.71, 95% CI 0.22; 1.19, $P = 0.004$ and β: −0.11, 95% CI −0.57; 0.36, $P = 0.66$). The developmental effect of cannabis use was independent of use of other drugs or current use of cannabis.
Conclusion: Early adolescence may be a critical period with regard to the psychotogenic effect of cannabis across geographical settings and ethnic groups.

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Key words: cannabis; adolescence; psychotic disorders; age of onset

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Significant outcomes

- Early onset of cannabis use is associated with a greater risk of developing psychotic symptoms.
- Findings regarding this association are not restricted to geographical settings and ethnic groups.

Limitations

- The study was cross-sectional.
- Self-report questionnaires were used to assess the psychosis outcome.

Introduction

Cannabis is the most widely used illicit substance in the world, particularly among young people. In the Netherlands, it was found that the proportion of cannabis users starting at age 13 years or younger increased from 21% to 41% between 1992 and 1998 (1). In several other European countries and in the USA, increasing drug use among young people has also been reported (2, 3). A growing body of evidence suggests that cannabis is associated with increased levels of positive symptoms (4) and constitutes a risk factor for psychotic outcomes including psychotic illness (5–8). In addition, it has been suggested that the psychotogenic effects of cannabis may be most profound after exposure during early adolescence, indicating the existence of a developmentally specific window of exposure in relation to psychosis (9, 10). Until now, however, the psychosis-enhancing effects of cannabis have only been shown in western populations, where reporting bias may be an issue (11).

Aims of the study

The aims of this study, therefore, were to i) cross sectionally investigate the association between cannabis use and positive psychotic experiences in

young people living in a non-western society and ii) investigate whether this association was moderated by age of onset. This is the first study in a non-western country investigating the association between cannabis and psychotic experiences in a multi-ethnic community.

Material and methods

Procedure and sample

Four hundred and seventy-two pupils (aged 12–23 years, mean age 16 years) were randomly selected from different schools in Trinidad (Republic of Trinidad and Tobago), an island located at the southern most position of the Caribbean islands, 11 km from the Venezuelan coast, and were asked to participate in the study. To obtain a representative sample of Trinidadian adolescents, participants were recruited through randomly selected (based on the geographical position of the school) vocational and governmental schools. Vocational and governmental schools are the main schools in Trinidad, and are attended by approximately 70% of all adolescents (12). Every school agreed to participate, and during a 1-day school visit, every student present at that time was invited to participate in the study and none of them refused. Questionnaires on cannabis use and psychotic symptoms were completed in the classroom under the supervision of a teacher. Of all collected questionnaires, 41 were incomplete. The study sample therefore consisted of 431 subjects.

Instruments

Use of cannabis and use of other drugs, including age of first use, were assessed using a self-report questionnaire. The questionnaire consisted of dichotomous items assessing life time (phrased as 'at least once') and current use of cannabis and life time and current use of other drugs. Age of first cannabis use was assessed as well. The Community Assessment of Psychic Experiences (CAPE), a self-report instrument, was used to assess positive psychotic experiences (10, 11 and 13). The CAPE has shown to be reliable and valid (13, 14). For the current analyses, the total score on the positive dimension was used as the psychosis outcome. To account for partial non-response, CAPE scores were weighted for the number of valid answers per dimension. These weighted CAPE scores were expressed as standardised scores.

Analyses

Multiple linear regression was used to examine the association between lifetime cannabis use (exposure variable) and psychotic symptoms (response variable). To investigate cannabis effects in association with the age of onset of cannabis use, the sample was divided *a priori* (on the basis of the group's mean age of onset of cannabis use of 13 years) in three groups as follows: i) no cannabis use; ii) cannabis use before 14 years and iii) cannabis use at or after the age of 14 years.

All analyses were *a priori* adjusted for age, school type (0 = average school; 1 = vocational school), ethnicity (0 = other; 1 = Indian; 2 = African), sex and in addition current use of cannabis and use of other drugs. Sensitivity analyses were conducted using the HOTDECK command in STATA (version 9.0) to examine whether missing data on the cannabis question in the questionnaire could have biased the findings.

Results

The final sample consisted of 431 adolescents and young adults. Mean age of the sample at the time of interview was 16.0 years (range 12–21), 239 (55%) were females and 27% of the individuals were attending vocational schools. Twenty-seven per cent was from Indian and 39% from African origin. The rate of lifetime cannabis use was 21% (n = 90) and of these, 34 had started their use before the age of 14 years (38% of the cannabis users) and 40 at or after the age of 14 years (answers on age of onset were missing for 16 subjects). The mean age of onset of cannabis use was 13.3 (range 7–19, SD 2.3). Current cannabis use was reported by 49% (n = 44) of the pupils with lifetime cannabis use. Lifetime use of other drugs was reported in 6% of the sample.

Overall, cannabis use was not associated with increased levels of psychotic symptoms (β = 0.14, 95% CI: −0.10;0.37, P = 0.25). However, there was a significant interaction between cannabis use and the age of first use, indicating that the effect of cannabis on the psychosis outcome was significantly stronger with early use of cannabis (F (1, 371) = 3.91, P = 0.05). Thus, the use of cannabis before the age of 14 years was significantly associated with higher levels of psychotic symptoms (β = 0.39, 95% CI: 0.04;0.74, P = 0.029). This association remained both large and statistically significant after adjustment for age, school type, ethnicity, sex, current use of cannabis and use of other drugs (Table 1). No such association was

Table 1. Effect of age of first cannabis use on positive psychotic symptoms (CAPE scores)

Adjustment	Age of first use*	CAPE scores (β†)	95% CI; *P*	Comparison early vs. old-age of onset
Not adjusted	Never used‡	0	–	
	≥14 years	0.01	−0.32;0.34; *P* = 0.95	
	<14 years	0.39	0.04;0.74; *P* = 0.029	
Adjusted§	Never used	0	–	*F* (1, 371) = 3.91,
	≥14 years	−0.11	−0.57;0.36; *P* = 0.66	*P* = 0.05¶
	<14 years	0.71	0.22;1.19; *P* = 0.004	

CAPE, Community Assessment of Psychic Experiences.

*The effect of age of first cannabis use, expressed dichotomously as before the age of 14 years or after the age of 14 years.

†Regression coefficient indicates change in CAPE positive symptom scores associated with different categories of age of first use.

‡Reference category.

§Adjusted for age, school type, ethnicity, sex, current use of cannabis and use of other drugs.

¶Statistical comparison between the effect sizes of the categories ≥14 years and <14 years by Wald test indicates that the cannabis effect size in the younger age group (<14 years) is significantly greater than in the older age group (≥14 years).

observed for the individuals who started their use of cannabis after the age of 14 years (Table 1).

Discussion

Sub-clinical psychotic symptoms as measured by the CAPE are of interest as they show longitudinal continuity with more severe states of psychotic illness (15). Furthermore, a recent study showed that cannabis may not only play a role in the onset of sub-clinical expression of psychosis, but also causes abnormal persistence of sub-clinical symptoms and eventually, as a consequence, need for psychiatric care (16). The results of this study confirm findings from two earlier epidemiological studies (9, 10) that early onset of cannabis use is associated with a greater risk to develop psychotic symptoms than later onset of use. The association between early exposure to cannabis and psychotic symptoms remained significant after adjustment for current use of cannabis and other drug use. In addition, this is the first study, to our knowledge, to show psychotogenic effects of early cannabis exposure in a non-western society, where cannabis use has a long, non-stigmatised history for medical and recreational use (17).

Based on the current findings, it may be argued that cannabis early exposure effects are developmental in nature and that they do not simply reflect effects of long-term exposure associated with earlier onset of use. In other words, a 10-year history of cannabis use may impact differentially on risk of psychosis depending on whether the current age of the subject is 22 or 32 years. Similar evidence comes from animal studies in which only Δ-9-tetrahydrocannabinol (THC, the principal component of cannabis) exposure during puberty, but not in adult rats, induced behavioural and cognitive changes (18). In addition, studies investigating the long-term effects of THC on cognition found similar developmental effects of cannabis exposure (19, 20). The fact that the endocannabinoid and the dopamine system are closely related (21) may partly explain why early adolescence in particular may be such a vulnerable period with respect to the adverse effects of THC. In rodents, THC facilitates dopamine transmission in different brain areas (22, 23). Chronic exposure to THC on the other hand, may result in a reduction of dopamine metabolism in the PFC (24). In addition, the Val allele (of the COMT Val158Met polymorphism), which is associated with higher levels of mesolimbic dopamine signalling and lower dopaminergic activity in the prefrontal cortex (PFC) (25), is also associated with increased sensitivity to the psychotic and cognitive effects of THC (26, 27). Schizophrenia has a postadolescent age of onset and is related to PFC dysfunction. As changes in synaptic dopamine activity in the PFC occur until adulthood, the PFC in particular may be sensitive to adverse environmental influences during puberty (28). A recent study by Tunbridge showed that COMT enzyme activity increases across the lifespan, and that COMT may play a functional role in the changes occurring in the PFC during adolescence (29). Therefore, in individuals with genetic vulnerability (e.g. carriers of the COMT Val158Met Val allele), early cannabis exposure may cause later psychosis by enhancing pre-existing dysregulation of the prefrontal and mesolimbic dopamine system (30). In addition, there is evidence that the effect of different environmental risk factors for psychosis may be additive (16) as was recently shown for early cannabis exposure and childhood trauma (31–33).

A methodological limitation of this study is that as symptoms and cannabis use were investigated cross sectionally, reverse causality cannot be excluded. However, previous studies have shown that although self-medication effects may in part contribute to the cannabis-psychosis relationship (34), they cannot explain the association entirely and cannabis is more likely to predict psychosis than vice versa (35). A second limitation is that cannabis use was assessed using self-report questionnaires under the supervision of a teacher, which may have yielded false negatives. Any false negative however, would have caused an under- rather than an over-representation of the actual effect size. In addition, cannabis use has a long

history for medical and recreational use in the Caribbean, which makes under-reporting unlikely.

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Declaration of interest

Jim van Os is a speaker or grant holder with Lilly, BMS, Lundbeck, Organon, Janssen-Cilag, GSK, Otsuka and AstraZeneca.

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