

Prospective cohort study of cannabis use, predisposition for psychosis, and psychotic symptoms in young people

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Abstract

Objective To investigate the relation between cannabis use and psychotic symptoms in individuals with above average predisposition for psychosis who first used cannabis during adolescence.

Design Analysis of prospective data from a population based sample. Assessment of substance use, predisposition for psychosis, and psychotic symptoms was based on standardised personal interviews at baseline and at follow up four years later.

Participants 2437 young people (aged 14 to 24 years) with and without predisposition for psychosis.

Main outcome measure Psychotic symptoms at follow up as a function of cannabis use and predisposition for psychosis at baseline.

Results After adjustment for age, sex, socioeconomic status, urbanicity, childhood trauma, predisposition for psychosis at baseline, and use of other drugs, tobacco, and alcohol, cannabis use at baseline increased the cumulative incidence of psychotic symptoms at follow up four years later (adjusted odds ratio 1.67, 95% confidence interval 1.13 to 2.46). The effect of cannabis use was much stronger in those with any predisposition for psychosis at baseline (23.8% adjusted difference in risk, 95% confidence interval 7.9 to 39.7, $P=0.003$) than in those without (5.6%, 0.4 to 10.8, $P=0.033$). The risk difference in the "predisposition" group was significantly greater than the risk difference in the "no predisposition" group (test for interaction 18.2%, 1.6 to 34.8, $P=0.032$).

There was a dose-response relation with increasing frequency of cannabis use. Predisposition for psychosis at baseline did not significantly predict cannabis use four years later (adjusted odds ratio 1.42, 95% confidence interval 0.88 to 2.31).

Conclusion Cannabis use moderately increases the risk of psychotic symptoms in young people but has a much stronger effect in those with evidence of predisposition for psychosis.

Introduction

There is increasing evidence that cannabis use may be a risk factor for psychotic symptoms.^{1,2} The possible causal nature of the association between cannabis and psychosis, however, is still a matter of debate, the main

discussion revolving around the role of predisposition for psychosis and adjustment for confounders.^{3,4}

We investigated prospectively whether cannabis use at baseline increases the risk of subsequent development of psychotic symptoms, whether any such increase in risk is higher in individuals with a predisposition for psychosis, and whether baseline expression of predisposition increases the risk for subsequent use of cannabis.

Methods

Sample

The study was part of the early developmental stages of the psychopathology (EDSP) study,⁵ in which data were collected on the prevalence, incidence, risk factors, comorbidity, and four year course of mental disorders, in a random regional representative population sample of adolescents and young adults aged 14-24 years. The EDSP study consists of a baseline survey in 1995, an assessment of a subsample in 1996-7, and a four year follow up of the total sample in 1999.⁵ The current analyses used the baseline and four-year follow up data. The study sample was randomly drawn from the respective population registry offices of the city and each of the 29 counties of Munich. At baseline 3021 participants were interviewed face to face in their homes by using a computer assisted method. An average of 42 months after the baseline investigations we analysed 2437 participants (response rate 81%).

Instruments

Participants were interviewed by trained psychologists using the Munich version of the composite international diagnostic interview (M-CIDI).⁶ At baseline and at follow up, participants additionally completed the self report symptom checklist (SCL-90-R)⁷ to screen for a broad range of psychopathological experiences including psychosis.

We used the "paranoid ideation" and "psychoticism" subscales of the symptom checklist to explore predisposition for psychosis at baseline and at follow up. Total scores of both subscales were added into a total score. Participants with total scores above the 90th

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Table 1 Patterns of cannabis use at baseline and psychotic symptoms at follow up. Figures are numbers (percentages) of participants

Cannabis use at baseline	Any psychotic symptom at follow up		At least two psychotic symptoms at follow up	
	Yes (n=424)	No (n=2013)	Yes (n=174)	No (n=2263)
Any use (≥5 times)	82 (19.3)	238 (11.8)	44 (25.3)	276 (12.2)
Cumulative frequency*:				
None	342 (80.7)	1775 (88.2)	130 (74.7)	1987 (87.8)
<1 times/month	13 (3.1)	69 (3.4)	5 (2.9)	77 (3.4)
3-4 times/month	18 (4.2)	62 (3.1)	10 (5.7)	70 (3.1)
1-2 times/week	17 (4.0)	40 (2.0)	7 (4.0)	50 (2.2)
3-4 times/week	12 (2.8)	21 (1.0)	8 (4.6)	25 (1.1)
Almost daily	22 (5.2)	46 (2.3)	14 (8.0)	54 (2.4)

*Some percentages do not total 100 because of rounding.

centile were considered as having a predisposition for psychosis, both at baseline and at follow up. We defined an outcome of psychosis as at least one (broad psychosis outcome) or at least two (narrow psychosis outcome) positive ratings on any of the 15 core psychosis items of the M-CIDI. To assess symptoms of depression at baseline and follow up we calculated a mean score of the ratings on the 28 items of the depression section of the composite diagnostic interview. We divided this into two groups at the 90th centile, yielding a measure of significant symptoms at both baseline and follow up.

Individuals with lifetime cannabis use of five times or more at baseline were considered as exposed to cannabis. Cannabis exposure at baseline was defined as lifetime cannabis use of five times or more (any use) and frequency of use (use during the period of heaviest use: no use; less than once a month; three to four times a month; once to twice a week; three to four times a week; almost daily). Cannabis use at follow up was analysed as cannabis use of five times or more during the four years to follow up (any use at follow up).

Statistical analyses

We used logistic regression models to assess the associations between any use of cannabis or frequency of use at baseline and psychotic symptoms at follow up. All analyses were adjusted for age, sex, socioeconomic status, urbanicity,⁸ experience of childhood trauma,⁹ and for predisposition for psychosis at baseline (see also bmj.com).

The population attributable fraction was derived from the associations between any use of cannabis and psychotic symptoms according to the M-CIDI at follow up (adjusted for demographics and trauma during childhood). This parameter gives a measure of the proportion of cases in participants with psychotic symptoms according to the M-CIDI at follow up that could have been prevented, assuming causality, had the exposure to cannabis been eliminated completely from the population.

Results

We followed up 2437 participants, of which 1251 (51.3%) were men. The mean age was 18.3 years (SD 3.3 years) at baseline and 21.8 years (3.4 years) at follow up. At four year follow up the cumulative lifetime incidence of at least one psychotic symptom was 424 (17.4%), irrespective of severity and impairment probe criteria, and 174 (7.1%) participants reported two or more psychotic symptoms. At baseline 320 (13.1%) admitted to any use of cannabis (five times or more) and 361 (14.8%) did so at follow up.

Any cannabis use at baseline increased the risk of psychotic symptoms according to the M-CIDI at follow up four years later in a dose-response fashion (tables 1-3), regardless of confounders, and with larger effect sizes for the narrowly defined psychosis outcome.

The effect of baseline cannabis use on the psychosis outcome according to the M-CIDI at follow up was much stronger in those with predisposition for psychosis at baseline (23.8% adjusted difference in risk) than in those without (5.6% adjusted difference in risk, table 4). The population attributable fraction was 6.2% for the total group and more than twice as large (14.2%) for the group with predisposition for psychosis at baseline.

Predisposition for psychosis at baseline did not significantly predict cannabis use at follow up four years later (odds ratio 1.42, 95% confidence interval 0.94 to 2.15, for the whole sample and 1.42, 95% confidence interval 0.88 to 2.31, for the subgroup with no cannabis use at baseline).

Discussion

Exposure to cannabis during adolescence and young adulthood increases the risk of psychotic symptoms later in life. The findings confirm earlier suggestions that this association is stronger for individuals with predisposition for psychosis^{2,10} and stronger for the more severe psychotic outcomes.^{2,10} Frequent use of

Table 3 Associations between frequency of cannabis use at baseline and any psychotic symptoms. Figures are odds ratios (95% confidence intervals)

Cumulative frequency of cannabis use	Unadjusted	Adjusted*
None†	1	1
<1/month	1.01 (0.55 to 1.86)	0.99 (0.53 to 1.84)
3-4 times/month	1.56 (0.91 to 2.68)	1.50 (0.86 to 2.62)
1-2 times/week	2.28 (1.28 to 4.09)	1.95 (1.07 to 3.55)
3-4 times/week	3.07 (1.49 to 6.31)	2.44 (1.16 to 5.13)
Almost daily	2.57 (1.52 to 4.34)	2.23 (1.30 to 3.84)
Linear trend‡	1.24 (1.15 to 1.35)	1.20 (1.10 to 1.31)

*Adjusted for age, sex, socioeconomic status, urbanicity, childhood trauma, and predisposition for psychosis at baseline.

†Reference category.

‡Increase in risk with one unit change in cannabis frequency.

Table 2 Associations between any cannabis use at baseline and psychotic symptoms at follow up. Figures are odds ratios (95% confidence intervals)

Cannabis exposure at baseline	Any psychotic symptom				At least two psychotic symptoms
	Unadjusted	Adjusted*	Additional adjustment†	Additional adjustment‡	Adjusted*
Any use (≥5 times)	1.79 (1.36 to 2.36)	1.69 (1.26 to 2.25)	1.67 (1.13 to 2.46)	1.53 (1.13 to 2.07)	2.23 (1.52 to 3.29)

*Age, sex, socioeconomic status, urbanicity, childhood trauma, and predisposition for psychosis at baseline.

†Also adjusted for other drug use, tobacco, and alcohol.

‡Also adjusted for predisposition for psychosis at follow up and depression at baseline and follow up.

Table 4 Interactions between any cannabis use and predisposition for psychosis

Cannabis use at baseline	No with psychosis outcome*	No without psychosis outcome*	Risk of psychotic symptoms at follow up	Difference in risk	
				Unadjusted	Adjusted† (95% CI)
No predisposition for psychosis at baseline					
None	294	1642	15%	6%	5.6% (0.4 to 10.8) P=0.033
Any (≥5 times)	59	216	21%		
Predisposition for psychosis at baseline‡					
None	47	133	26%	25%	23.8% (7.9 to 39.7) P=0.003
Any (≥5 times)	23	22	51%		

*Numbers total 2436 because of one missing value on predisposition for psychosis at baseline.

†Age, sex, socioeconomic status, urbanicity, childhood trauma, and predisposition for psychosis at follow up. Test for additive interaction 18.2% adjusted difference in risk (95% confidence interval 1.6 to 34.8), P=0.032 (tests whether risk difference in "predisposition" group is significantly greater than risk difference in "no predisposition" group).

‡Total score ≥90th centile on "paranoid ideation" and "psychoticism" subscales of symptom checklist.

cannabis was associated with higher levels of risk in a dose-response fashion. Associations were independent of other variables known to increase the risk for psychosis. Also, the effect of cannabis remained significant after we corrected for baseline use of other drugs, tobacco, and alcohol. Finally, the data did not support the self medication hypothesis as baseline predisposition for psychosis did not significantly predict cannabis use at follow up.

Strengths and weaknesses

We examined psychotic symptoms according to the M-CIDI at follow up in a non-clinical sample. Symptoms were more prevalent than psychotic disorders defined according to the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition. Such symptoms are known to be on the same continuum of experiences as more severe states of psychosis, such as schizophrenia.^{11 12} Established risk factors for schizophrenia, such as urbanicity and familial predisposition, also affect the occurrence of psychotic symptoms.^{13 14} Our results confirm those from three previous studies that showed that exposure to cannabis plays a part not only in the expression of psychotic disorder but also in the emergence of less severe psychotic experiences.^{2 10 15}

At baseline we used self reported psychotic experiences on the symptom checklist to determine predisposition for psychosis, whereas at follow up we used the M-CIDI to determine psychosis outcome. In

the group with predisposition for psychosis at baseline, any effect of cannabis can thus be interpreted as psychosis persisting from baseline to follow up (if we assume that the two measures of psychosis are identical), rather than an effect of transition from expression of predisposition at baseline to expression of overt symptoms at follow up. Although both explanations would be equally important, adjustment for the effect of the follow up equivalent of the baseline measure of predisposition for psychosis did not change the observed association between cannabis and psychotic symptoms according to the M-CIDI, indicating that the effect of cannabis can be interpreted as onset of clinical psychosis outside the continuity between the measure of predisposition for psychosis at baseline and follow up. In addition, cannabis also had a significant effect on psychotic symptoms in the group without predisposition for psychosis at baseline, albeit of smaller effect.

This work is part of the early developmental stages of psychopathology (EDSP) study. Principal investigators are Hans-Ulrich Wittchen and Roselind Lieb. Current or former staff members of the EDSP group include Kirsten von Sydow, Gabriele Lachner, Axel Perkonig, Peter Schuster, Michael Höfler, Holger Sonntag, Esther Beloch, Martina Fuetsch, Elzbieta Garczynski, Alexandra Holly, Barbara Isensee, Chris Nelson, Hildegard Pfister, Victoria Reed, Andrea Schreier, and Petra Zimmermann. Scientific advisers are Jules Angst (Zurich), Jürgen Margraf (Basel), Günther Esser (Potsdam), Kathleen Merikangas (NIMH, Bethesda), Jim van Os (Maastricht), and Ron Kessler (Harvard, Boston).

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Competing interests: None declared.

Ethical approval: The local ethics committee approved the study.

What is already known on this topic

It is generally accepted that cannabis use is strongly associated with psychosis

We do not know whether the association is causal or whether those with a predisposition for psychosis are particularly at risk

What this study adds

Cannabis use in young people moderately increased the risk of developing psychotic symptoms

The risk for the onset of symptoms was much higher in young people with a predisposition for psychosis

Predisposition psychosis at baseline did not predict cannabis use at follow up, thus refuting the self medication hypothesis

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Cognitive behaviour therapy for adolescents with chronic fatigue syndrome: randomised controlled trial

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Abstract

Objective To evaluate the efficacy of cognitive behaviour therapy for adolescents aged 10-17 years with chronic fatigue syndrome.

Design Randomised controlled trial.

Setting Department of child psychology.

Participants 71 consecutively referred patients with chronic fatigue syndrome; 36 were randomly assigned to immediate cognitive behaviour therapy and 35 to the waiting list for therapy.

Intervention 10 sessions of therapy over five months. Treatment protocols depended on the type of activity pattern (relatively active or passive). All participants were assessed again after five months.

Main outcome measures Fatigue severity (checklist individual strength), functional impairment (SF-36 physical functioning), and school attendance.

Results 62 patients had complete data at five months (29 in the immediate therapy group and 33 on the waiting list). Patients in the therapy group reported significantly greater decrease in fatigue severity (difference in decrease on checklist individual strength was 14.5, 95% confidence interval 7.4 to 21.6) and functional impairment (difference in increase on SF-36 physical functioning was 17.3, 6.2 to 28.4) and their attendance at school increased significantly (difference in increase in percentage school attendance was 18.2, 0.8 to 35.5). They also reported a significant reduction in several accompanying symptoms. Self reported improvement was largest in the therapy group.

Conclusion Cognitive behaviour therapy is an effective treatment for chronic fatigue syndrome in adolescents.

Introduction

Patients with chronic fatigue syndrome have debilitating unexplained severe fatigue that is not the result of an organic disease or ongoing exertion and is not alleviated by rest. Symptoms last for at least six months and are accompanied by other symptoms like muscle pain and unrefreshing sleep.^{1,2} This condition can

occur in adults and adolescents.³ Several randomised controlled trials have shown that cognitive behaviour therapy is effective in adults.^{4,5} To date, however, there have been no published controlled studies on such therapy for adolescents, though one uncontrolled study suggested that such a behavioural approach can reduce fatigue in adolescents.⁶ Development of potentially effective interventions is especially important in young people to avoid prolonged absence from school and restricted social activities, which threaten healthy development.⁷⁻⁹

Methods

We studied the efficacy of cognitive behaviour therapy for adolescents with chronic fatigue syndrome by comparing outcome in those randomly assigned to immediate therapy with outcome in those who were assigned to the waiting list for therapy. We used two treatment protocols: one for patients with a passive physical activity pattern and one for relatively active patients.^{4,10,11} We hypothesised that fatigue severity, functional impairment, and school absence would decrease significantly more in those assigned to immediate therapy.

Patients

As part of the usual care all consecutive patients with a major complaint of fatigue referred to the paediatrics outpatient clinic between October 1999 and October 2002 were assessed by means of a detailed history and physical and laboratory examinations. Patients were eligible if they were between 10 and 17.2 years of age (to allow the older participants to complete therapy before their 18th birthday) and met the US Centers for Disease Control Prevention criteria for chronic fatigue syndrome.¹ Severe fatigue and severe functional impairment were defined as scores of 40 or more on the fatigue severity subscale of the checklist individual



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