

# Cannabis use and age at onset of symptoms in subjects at clinical high risk for psychosis

Dragt S, Nieman DH, Schultze-Lutter F, van der Meer F, Becker H, de Haan L, Dingemans PM, Birchwood M, Patterson P, Salokangas RKR, Heinimaa M, Heinz A, Juckel G, Graf von Reventlow H, French P, Stevens H, Ruhrmann S, Klosterkötter J, Linszen DH, on behalf of the EPOS group. Cannabis use and age at onset of symptoms in subjects at clinical high risk for psychosis.

**Objective:** Numerous studies have found a robust association between cannabis use and the onset of psychosis. Nevertheless, the relationship between cannabis use and the onset of early (or, in retrospect, prodromal) symptoms of psychosis remains unclear. The study focused on investigating the relationship between cannabis use and early and high-risk symptoms in subjects at clinical high risk for psychosis.

**Method:** Prospective multicenter, naturalistic field study with an 18-month follow-up period in 245 help-seeking individuals clinically at high risk. The Composite International Diagnostic Interview was used to assess their cannabis use. Age at onset of high risk or certain early symptoms was assessed retrospectively with the Interview for the Retrospective Assessment of the Onset of Schizophrenia.

**Results:** Younger age at onset of cannabis use or a cannabis use disorder was significantly related to younger age at onset of six symptoms ( $0.33 < r_s < 0.83$ ,  $0.004 < P < 0.001$ ). Onset of cannabis use preceded symptoms in most participants.

**Conclusion:** Our results provide support that cannabis use plays an important role in the development of psychosis in vulnerable individuals. Cannabis use in early adolescence should be discouraged.

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Key words: psychosis; cannabis; prodromal; age at onset

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## Significant outcomes

- Earlier lifetime cannabis use or cannabis use disorder onset age is associated with earlier appearance of a range of symptoms in individuals at clinical high risk of psychosis.
- Onset of cannabis use preceded symptoms in most participants.
- Cannabis use did not predict future transition to psychosis.

### Limitations

- It is clear that more definitive conclusions require larger samples.
- The study was limited by the retrospective nature of the information regarding onset of high-risk symptoms assessed with the Interview for the Retrospective Assessment of the Onset of Schizophrenia (IRAOS).
- Assessment of cannabis use was based solely on participants report.

### Introduction

Despite the large body of literature on cannabis and psychosis, their relation is not an exclusive one. Retrospective first-episode psychosis studies found that cannabis use precedes the onset of first positive symptoms of schizophrenia (1–3), and that preonset cannabis use may hasten the onset of psychotic as well as prodromal symptoms – the more so the earlier consumption starts (4). These findings were later corroborated by prospective studies that report a robust association between cannabis use and the onset of psychosis (5–9), prodromal or psychotic-like symptoms (10–12), and in non-clinical dimensions of psychosis, respectively (13). While these studies suggest that age at onset of cannabis use plays an important role in the development of psychosis, studies investigating the causality and the direction of causality of the relationship between cannabis use and psychosis led to inconsistent results. Thus, the question remains whether cannabis use precedes prodromal symptoms (and possibly increases prodromal symptoms) or if it is a consequence of prodromal symptoms (suggesting a self-medication strategy). Different hypotheses on causality have been formulated. In earlier research, other factors related to schizophrenia, such as male gender, worse socioeconomic status, better premorbid childhood social adjustment, were found to be associated with cannabis use in first-episode schizophrenia patients (14).

Previous studies describe that transient delusions as well as hallucinations and other clinical symptoms were repeatedly reported by cannabis users, with anxiety and panic reactions, depersonalization, derealization, and depression being particularly frequent (15–20). Furthermore, tiredness, low motivation, social withdrawal, and several effects on cognition were reported (17, 18). All of these symptoms, however, have also been frequently reported to occur within the prodrome of first-episode psychosis (21). The present study addresses the relationship between cannabis and developing psychosis in a 18-month follow-up study of a large European population of clinical high risk (CHR) individuals (22, 23). We investigated the time-

related relationship between cannabis use and non-psychotic symptoms potentially prodromal for psychosis. Thereby, we focused on symptoms, frequently reported as both prodromal symptoms of psychosis and as psychopathological effects of cannabis use.

### Aims of the study

The aims of this study, therefore, were to investigate whether i) onset of cannabis use or a cannabis use disorder at a younger age relates to onset of the selected symptoms at a younger age and whether ii), in case of such a relationship, cannabis use precedes the onset of these symptoms. Furthermore, the particular effect of cannabis use on transition to psychosis was investigated.

### Material and methods

#### Recruitment

Between August 2002 and April 2006, data were collected from 245 help-seeking patients (age 16–35) who met ‘ultra-high risk’ (UHR) and/or ‘cognitive disturbances’ (COGDIS) criteria and agreed to participate in the European Prediction of Psychosis Study, EPOS (22, 23). EPOS is a European collaboration of six centers in four countries: Germany, Finland, the Netherlands, and England. Referrals to the early detection services originated from a range of sources including psychiatrists, psychologists, GPs, outreach clinics, counselling services, and teachers or was self-initiated.

Inclusion criteria comprised of UHR criteria as assessed by the ‘Structured Interview for Prodromal Syndromes’ (SIPS 3.0) (24) and COGDIS as assessed by the ‘Bonn Scale for the Assessment of Basic Symptoms – Prediction List’ (BSABS-P), an abbreviated version of the ‘Schizophrenia Prone-ness Instrument, Adult version’ (SPI-A) (25).

The UHR approach consists of three alternative criteria:

- i) Attenuated psychotic symptoms defined by at least one of the following symptoms with SIPS

score 'moderate' to 'severe but not psychotic' (3–5), appearing several times per week for at least 1 week within the last 3 months: unusual thought content/delusional ideas, suspiciousness/persecutory ideas, grandiosity, perceptual abnormalities/hallucinations, disorganized communication, and odd behaviour/appearance;

- ii) Brief limited intermittent psychotic symptoms defined by hallucinations, delusions, or formal thought disorders occurring within the last 3 months and resolving spontaneously within 1 week scoring 'severe and psychotic' (6) on the SIPS and achieving at least 'moderate' score on the respective item of the Positive and Negative Syndrome Scale for Schizophrenia (26);
- iii) Genetic risk and functional deterioration defined by a 30% or greater reduction in the Global Assessment of Functioning Scale, modified version (GAF-M) (27, 28), as compared to the highest level of previous functioning for at least 1 month within the previous year in combination with a first- or second-degree relative with a history of any DSM-IV psychotic disorder (29) or a DSM-IV schizotypal personality disorder of the index person.

Cognitive disturbances requires the presence of at least two of nine cognitive basic symptoms (BS) of at least 'moderate' severity ( $\geq 3$ ) during the last 3 months and, independent of severity, first occurrence at least 1 year before intake: inability to divide attention, thought interference, pressure, and blockage, disturbances of receptive and of expressive speech, disturbance of abstract thinking, unstable ideas of reference, captivation of attention by details of the visual field.

Exclusion criteria were i) a low verbal IQ (IQ < 85); ii) past or present psychotic episode lasting longer than 1 week, i.e., fulfilling DSM-IV criteria of a Brief Psychotic Episode for at least 7 days consecutive, assessed by the 'Structured Clinical Interview for DSM-IV, (SCID)' (29); and iii) symptoms relevant for inclusion arising from a known general medical disorder or drugs or alcohol dependency. Subjects who used cannabis were asked whether they had a period of symptoms in which they did not use cannabis; if not, they were asked to stop using for 2 weeks to see if symptoms continued. If a significant reduction or even full remission was observed, the at-risk symptom in question would not be considered an expression of a CHR state, while it would be considered one, if the symptom remained or even

increased in severity. Participants were not included in the study if the at-risk symptoms remitted when cannabis use was ceased.

Subjects who used hard drugs (e.g., cocaine, heroin, XTC, speed, and magic mushrooms) were excluded. On account of the naturalistic design of the present study, antipsychotic medication was not considered an exclusion criterion.

The mean observation period of the study was 431.3 days (SD, 10.9 days; median, 548.0 days); outcome at month 18 was known for 183 participants. At that time, 37 subjects had developed psychosis; none was diagnosed as substance-related psychosis (23). The instantaneous incidence rate of transition to psychosis after 6, 9, 12, and 18 months was 7%, 11%, 14%, and 19%, respectively (22). The mean time to transition from baseline examination was 496.8 days [SE, 8.5 days; 95% confidence interval (CI), 480.2–513.6] (23).

The investigation was carried out in accordance with the latest version of the Declaration of Helsinki. The study design was approved by the Research and Ethical Governance Committees of all participating centers. After complete description of the study to the subjects, written informed consent was obtained.

### Instruments

The Composite International Diagnostic Interview (CIDI) was used to collect data on cannabis use in the UHR group. The CIDI is a comprehensive, fully standardized, instrument for assessment of mental disorders according to the definitions and criteria of DSM-IV. Good reliability and validity of the CIDI have been reported (30). To account for the reported dose–response relationship, subjects with lifetime cannabis use (LC) and subjects with a cannabis use disorder were analyzed separately. LC was defined as ever having used more than five times. Cannabis use disorders (CD), i.e., cannabis abuse or dependence, were assessed according to DSM-IV criteria.

The 'Interview for the Retrospective Assessment of the Onset of Schizophrenia, IRAOS' assesses early signs and prodromal symptoms and documents time of first occurrence, presence, and course of symptoms with sufficient reliability (31). IRAOS allows a detailed and valid qualitative description of the onset and early course of the disease including prodromal, specific, and non-specific symptoms. Nine early and high-risk symptoms were employed for statistical analyses based on previous research findings examining cannabis use and mental health (15–20): anxiety, avoiding contact, depersonalization, depressed mood, derealization, impairment of

memory, weakness of thinking and concentration, persecutory ideas, and hallucinations (in any modality). While the first seven symptoms are rather unspecific early signs, the last two are part of the UHR criteria and thus considered as CHR symptoms. For example, the symptom weakness of focussed thinking is assessed with the following question: ‘Were you (the patient) ever so distracted that you were unable to follow your own thoughts or aim your thoughts on a specific point in time?’ The symptom avoiding contact is assessed with the following questions: ‘Have you (the patient) ever withdrawn from contact or did you avoid contact with others? Were you distrustful to others in general?’

Premorbid adjustment was assessed with the Premorbid Adjustment Scale (PAS) (32). We only used the childhood (up through age 11) PAS scores for the analyses to capture premorbid functioning before the onset of substance use disorders and psychosis. One subject with LC before age 11 was excluded from premorbid adjustment analyses. The childhood PAS includes two items for social adjustment and two items for academic adjustment. Each item is scored from 0 (good adjustment) to 6 (poor adjustment). Ratings for ‘Sociability and Withdrawal’ and ‘Peer Relationships’ were averaged to obtain a composite measure of social adjustment, and ‘Scholastic performance’ and ‘Adaptation to School’ were averaged to obtain a measure of academic adjustment.

#### Procedure

Following referral to one of the participating early detection centers, patients were routinely interviewed by a psychiatrist and/or a psychologist for EPOS intake and exclusion criteria. If eligible, the patient was informed about EPOS and asked to sign informed consent. At EPOS baseline (22), the complete SIPS, BSABS-P, and SCID-I as well as IRAOS and CIDI drug modules were conducted among other scales. Participants were followed up with the same scales for 18 months with a follow-up assessment every 9 months (22, 23).

#### Statistical analysis

Data were analyzed employing the Statistical Package for the Social Sciences (SPSS 16.0, Chicago, IL, USA). Cannabis users and non-users were compared with respect to age, gender, family history of psychosis, positive symptoms, negative symptoms, global functioning, and cognitive basic symptoms. *T* test and chi-square statistics for continuous and categorical variables,

respectively, were used. For ordinal data (e.g., SIPS and BSABS items), a non-parametric alternative (Mann–Whitney *U* test) was used.

For our main hypothesis, we employed Spearman’s Rho correlation coefficients to test for non-parametric correlations; the LC and CD groups were considered separately. The variables gender, PAS social adjustment, PAS academic adjustment, and alcohol use disorder were introduced as covariates in the model, because the variables may be confounding factors.

We corrected for multiple comparisons with the Bonferroni technique that set the critical alpha level at  $\alpha = 0.006$ .

Differences in reported IRAOS symptoms and age at onset of symptoms between the cannabis using and non-cannabis using groups were compared. For this analysis, we used a one-sample *t* test with a test value of zero to test significance of the mean differences in years between the onset of the symptom and the onset of cannabis use.

We investigated the chronology symptoms and onset of LC and CD for all subjects using cannabis in two different ways. First, by using a *t* test for paired samples comparing mean age at onset of cannabis use and mean age at onset of symptoms. Second, we divided LC subjects and CD subjects in three groups with onset of cannabis use earlier than the symptom, in the same year as the symptom or later than the symptom. We used a chi-square goodness-of-fit test to indicate whether significant difference was present in the proportion of LC subjects and CD subjects in the three groups, compared to the assumption that all groups are equal. This assumption was made based on previous research (2, 3).

The role of cannabis use on transition to psychosis was investigated with a Kaplan–Meier survival analysis, using log-rank test for group comparisons, for which *P*-values of  $<0.05$  were considered significant.

## Results

### General characteristics

Complete baseline data of relevant instruments were available for 242 of the 245 participants in EPOS. The CHR group was divided into cannabis users (LC) and non-cannabis users (see Fig. 1). Of the 242 participants, 102 (42.0%) had used cannabis more than five times during their life. Of these 102 LC subjects, 75 participants (73.5%) had used cannabis in the past year prior to baseline, 26 participants (25.5%) even in the month preceding baseline. The mean age at onset of cannabis use

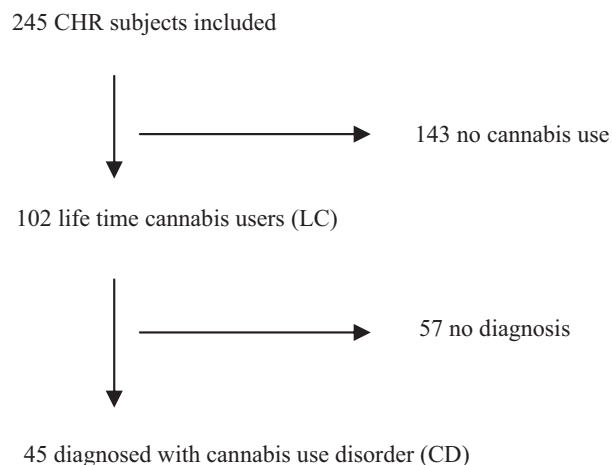


Fig. 1. Flowchart EPOS.

was 17.3 years (range 9–30, SD 3.5). Of the 243 participants, 45 (18.4%) were diagnosed with a cannabis use disorder (CD). The mean age at onset of cannabis dependence or abuse was 17.9 years (range 14–26, SD 3.0), and 86.7% of these subjects were male.

Of the LC group, 68.6% were male compared to 49.3% of the non-users ( $\chi^2 = 8.3$ ;  $df = 1$ ,  $P = 0.004$ ,  $\phi = -0.193$ ). In addition, LC showed a slightly higher total of the SIPS positive symptoms that did not reach statistical significance. Thus, except for gender, LC subjects and non-users were comparable in terms of demographics and clinical variables (Table 1).

Medication prescription

Of the 243 participants 114 did not use medication at baseline, 32 used antipsychotics, 46 used antidepressants, and 22 had a combination of antidepressants and antipsychotics. There was no significant differences in medication prescription between cannabis users and non-users ( $\chi^2 = 6.4$ ;  $df = 4$ ,  $P = 0.17$ ).

Transition rate

Of the 37 transitioned participants, 15 (40.5%) reported LC. There was no significant relationship between cannabis use and transition to psychosis (log-rank test  $\chi^2 = 1.37$ ,  $P = 0.24$ ) or between a diagnosis of a cannabis use disorder and transition to psychosis (log-rank test  $\chi^2 = 0.58$ ,  $P = 0.45$ ).

Age at onset of symptoms and LC or CD

Table 2 shows correlations between age at onset of each symptom and age at onset of LC.

Table 1. Baseline comparison of cannabis users and non-users (if not otherwise indicated mean and SD are given)

| Characteristic                             | Users (LC)<br>(n = 102) | Non-users<br>(n = 141) |
|--|-------------------------|------------------------|
| General characteristics                    |                         |                        |
| Age  | 22.9 (4.3)              | 22.3 (5.7)             |
| Sex (% male)*                              | 68.6                    | 49.3                   |
| Family history of psychosis (%)            | 21.9                    | 18.1                   |
| Social adjustment (PAS)                    | 3.3 (2.9)               | 2.9 (2.7)              |
| Academic adjustment (PAS)                  | 3.6 (2.4)               | 3.2 (2.3)              |
| Alcohol use disorder (%)**                 | 48.0                    | 18.6                   |
| Baseline symptomatology                    |                         |                        |
| SIPS positive symptoms                     | 10.3 (4.7)              | 9.1 (4.1)              |
| Unusual thought content/delusional ideas   | 3.2 (1.7)               | 3.0 (1.7)              |
| Suspiciousness/persecutory ideas           | 2.7 (1.6)               | 2.4 (1.7)              |
| Grandiose ideas                            | 0.7 (1.2)               | 0.6 (1.2)              |
| Perceptual abnormalities/hallucinations    | 2.5 (1.5)               | 2.2 (1.6)              |
| Disorganized communication                 | 1.3 (1.3)               | 1.0 (1.4)              |
| SIPS negative symptoms                     | 11.7 (6.4)              | 11.8 (6.7)             |
| Global functioning (GAF) current           | 51.3 (11.6)             | 50.8 (11.8)            |
| Global functioning (GAF) highest past year | 65.1 (14.3)             | 65.5 (13.8)            |
| COGDIS (total of the nine items)           | 12.4 (6.9)              | 10.9 (7.8)             |

PAS, premorbid adjustment scale, childhood section; COGDIS, cognitive disturbances; LC, lifetime cannabis use; SIPS, structured interview for prodromal syndromes.

\*Significant ( $P = 0.004$ ), \*\*Significant ( $P = 0.0001$ ).

Table 2. Correlation between age at onset of symptoms and age at onset of lifetime cannabis use (LC)

| Symptom                                | n (%)     | Statistics |          | Adjusted statistics** |          |
|--|-----------|------------|----------|-----------------------|----------|
|  |           | $r_s$      | $P$      | $r_s$                 | $P$      |
| Anxiety                                | 65 (63.7) | 0.55       | <0.0005* | 0.48                  | <0.0005* |
| Avoiding contact                       | 65 (63.7) | 0.37       | 0.002*   | 0.39                  | 0.002*   |
| Depersonalization                      | 20 (19.6) | 0.57       | 0.008    | 0.55                  | 0.029    |
| Depressed mood                         | 83 (81.4) | 0.33       | 0.003*   | 0.32                  | 0.004*   |
| Derealization                          | 35 (34.3) | 0.58       | <0.0005* | 0.67                  | <0.0005* |
| Impairment of memory                   | 24 (23.5) | 0.57       | 0.003*   | 0.53                  | 0.017    |
| Weakness of thinking and concentration | 72 (70.6) | 0.51       | <0.0005* | 0.44                  | <0.0005* |
| Hallucinations                         | 23 (22.5) | 0.47       | 0.022    | 0.48                  | 0.039    |
| Persecutory ideas                      | 8 (7.8)   | 0.55       | 0.156    | 0.41                  | 0.425    |

$r_s$  = spearman correlation coefficient.

\*Correlation is significant at the 0.006 level (two-tailed).

\*\*Adjusted for potential confounders: gender, PAS social adjustment, PAS academic adjustment, and alcohol use disorder.

PAS, premorbid adjustment scale.

After adjustment for potential confounders (gender, PAS social adjustment, PAS childhood adjustment, and alcohol use disorder), younger age at onset of LC was significantly related to younger age at onset of the symptoms anxiety, avoiding contact, depressed mood, derealization, and weakness of thinking and concentration.

Additionally, after adjustment for potential confounders, younger age at onset of CD was significantly related to younger age at onset of the symptoms anxiety ( $r_s = 0.70$ ,  $P \leq 0.0005$ ,

Table 3. Comparison of mean ages at onset of cannabis use (CU) and symptoms in clinical high risk subjects with lifetime cannabis use (LC)

| Symptom                                | Mean age ± SD (years) CU | Mean age ± SD (years) symptom | <i>n</i> | <i>P</i> | <i>t</i> |
|--|--------------------------|-------------------------------|----------|----------|----------|
| Anxiety                                | 17.7 ± 3.8               | 18.9 ± 5.9                    | 65       | 0.072    | 1.83     |
| Avoiding contact                       | 17.4 ± 3.8               | 19.3 ± 5.9*                   | 65       | 0.010    | 2.67     |
| Depersonalization                      | 16.4 ± 3.6               | 17.9 ± 4.9                    | 20       | 0.12     | 1.65     |
| Depressed mood                         | 17.3 ± 3.2               | 18.9 ± 4.6**                  | 83       | 0.003    | 3.06     |
| Derealization                          | 16.4 ± 3.5               | 19.3 ± 4.8**                  | 35       | <0.0005  | 4.82     |
| Impairment of memory                   | 16.9 ± 3.4               | 19.9 ± 4.3**                  | 24       | 0.002    | 3.58     |
| Weakness of thinking and concentration | 17.6 ± 3.7               | 19.9 ± 5.2**                  | 72       | <0.0005  | 3.96     |
| Hallucinations                         | 16.0 ± 2.3               | 19.6 ± 3.8**                  | 23       | <0.0005  | 4.90     |
| Persecutory ideas                      | 18.4 ± 3.2               | 22.9 ± 3.9*                   | 8        | 0.019    | 3.02     |

\**P* < 0.05, \*\**P* < 0.006.

Table 4. Percentage of lifetime cannabis users (LC) with onset of cannabis use ‘earlier than,’ ‘in the same year as,’ or ‘later than’ onset of symptom

| Symptom                                | Earlier than symptom | In same year as symptom | Later than symptom | <i>n</i> | <i>P</i> | $\chi^2$ |
|--|----------------------|-------------------------|--------------------|----------|----------|----------|
| Anxiety                                | 61.2**               | 13.4                    | 25.4               | 65       | <0.0005  | 22.3     |
| Avoiding contact                       | 61.8**               | 10.3                    | 27.9               | 65       | <0.0005  | 27.2     |
| Depersonalization                      | 60.0*                | 25.0                    | 15.0               | 20       | 0.035    | 6.7      |
| Depressed mood                         | 57.5**               | 14.9                    | 27.6               | 83       | <0.0005  | 25.5     |
| Derealization                          | 63.0**               | 10.8                    | 16.2               | 35       | <0.0005  | 26.5     |
| Impairment of memory                   | 80.0**               | 12.0                    | 8.0                | 24       | <0.0005  | 22.8     |
| Weakness of thinking and concentration | 67.1**               | 13.2                    | 19.7               | 72       | <0.0005  | 39.6     |
| Hallucinations                         | 73.9**               | 21.7                    | 4.3                | 23       | <0.0005  | 18.1     |
| Persecutory ideas                      | 90.0*                | 0                       | 10.0               | 8        | 0.034    | 4.5      |

\**P* < 0.05, \*\**P* < 0.006.

*n* = 34), avoiding contact ( $r_s = 0.58$ , *P* = 0.002, *n* = 31), impairment of memory ( $r_s = 0.84$ , *P* = 0.001, *n* = 16), and weakness of thinking and concentration ( $r_s = 0.57$ , *P* = 0.001, *n* = 34). Effects were more pronounced in subjects with a cannabis use disorder.

Chronology of the symptoms

The mean age at onset of LC was younger than the mean age at onset of the symptoms (Table 3). The comparison of group means shows the general trends. In order to clarify the temporal order in individual cases, we looked at percentage of subjects with onset of LC before, within the same year, and after onset of the selected symptoms. In support of group analyses, most subjects reported an earlier onset of cannabis use compared to symptom onset (Table 4).

Discussion

Our main finding is that earlier age at onset of cannabis use is associated with earlier appearance

of a range of symptoms in cannabis using individuals at CHR of psychosis. In our sample of CHR subjects, the association we found could not be attributed to gender, premorbid social adjustment, premorbid academic adjustment, and alcohol use disorder. The most robust associations were found between age at onset of cannabis use and age at onset of the symptoms anxiety, derealization, and weakness of thinking and concentration. Our results are consistent with previous reports on associations between cannabis use and these symptoms (15, 16, 18).

Secondly, our results indicated that most participants started using cannabis prior to the appearance of the examined nine symptoms. These findings are different from the results reported by Hambrecht and Häfner (3). In a group of first-episode schizophrenia patients, they differentiated three, equally large, groups of patients, with onset of substance abuse before, during, and after the onset of first (prodromal) symptom of schizophrenia as defined by the IRAOS. However, they did find that onset of first negative symptom and first positive symptom was after onset of substance abuse.

No differences were found between demographic and clinical characteristics of cannabis users and non-users at baseline, as well as for transition rates to psychosis. These findings are consistent with previous research in the CHR population (33–35) except for one study that reported an increased 1-year transition rate of cannabis abusers in an UHR sample (36). Recently, in a large sample of 291 CHR subjects, a history of any substance abuse (irrespective of type of substance) was found to contribute uniquely to the prediction of psychosis (37).

In summary, our findings suggest that in a cannabis using CHR subsample, cannabis use at an earlier age is associated with onset of at least some early and CHR symptoms at an earlier age and that onset of cannabis use precedes the onset of these symptoms in most cases. This is in concordance with a number of studies that found a dose-response relationship between cannabis use and psychosis, with findings suggesting that cannabis use at a younger age predicts psychotic development later in life (9, 12, 38). However, psychotic symptoms in those who had never used cannabis before the onset of psychotic symptoms also predicted future cannabis use (39).

The relationship between age at onset of cannabis use and early and CHR symptoms may be explained in several ways. Firstly, it could be that cannabis use and the selected symptoms share a common underlying factor such as shared environmental exposure and/or genetic risk factors.

This could be interpreted as a coincidental association of two discrete psychiatric disorders that peak during the same developmental stage. Alternatively, there could be a gene–environment interaction which suggests that a role of some genes is to influence vulnerability to environmental pathogens (in this case; cannabis use). This hypothesis is supported by findings of Caspi et al. (40) that suggest such an interaction of a functional polymorphism in the catechol-O-methyltransferase gene with adolescent cannabis use (i.e., if subjects had used cannabis before age 15 or if they were at least monthly cannabis users by age 18) on developing adult psychosis (i.e., measured at age 26). This was replicated in further research (41) and suggests that age is a crucial mediator in the effect of cannabis on psychosis, which was also reflected in our results.

A second explanation could be that there is a bi-directional and partial causal relationship. The development of early symptoms, e.g., anxiety or depression, could encourage the use of cannabis; the self-medication theory. Subsequently, the cannabis use itself could instigate positive high-risk symptoms, i.e., hallucinations or persecutory ideas. It has previously been reported that patients with psychotic disorders used cannabis mainly for affect regulation and socialization, despite the awareness that cannabis use exacerbates positive symptoms (19). Thus, patients may use cannabis for reasons of enhancing positive affect and for relief of dysphoria and anxiety and, in consequence, provoke other symptoms including positive psychotic symptoms.

These two alternative explanations have different implications for our understanding of the pathophysiology of psychotic disorders and for the possibility of intervening to prevent the onset of psychosis. Our results seem to support the first explanation with a hypothesis of coincidental association of two discrete psychiatric disorders that peak during the same developmental stage. However, additionally, there may be a critical developmental window during adolescence when cannabis exposure contributes to the etiology of schizophrenia or psychotic development. Further research might find clear genetic markers making it possible to screen vulnerability for a cannabis-linked pathway to psychosis.

Our results do not support the second explanation of a self-medication theory as, in the majority of participants, cannabis use preceded not only the onset of high-risk symptoms but also of early symptoms such as anxiety, depressed mood, and even avoiding contact. Moreover, our results suggest that cannabis use precedes the onset of

all (high-risk) symptoms and possibly elicits these symptoms in vulnerable subjects at an earlier stage.

There are limitations to this study. Firstly, although we employed a large research sample, the number of subjects who used cannabis and experienced the symptoms depersonalization, hallucinations, impairment of memory, and persecutory ideas was small. To draw firmer conclusions, a larger sample of cannabis users is required. Secondly, the study was limited by the retrospective nature of the information regarding onset of cannabis use and symptoms. Responses were dependent on participant's recall of the time period that cannabis use and early as well as CHR symptoms began. It is possible that retrospective reports are not reliable, although previous studies show good reliability with retrospective recollection (42, 43). In future studies, a larger sample of cannabis using individuals with a CHR state for developing psychosis would be useful to clarify any causal relationship between cannabis use and development of psychosis.

Although cannabis use had no direct impact on the transition to psychosis within the 18-month follow-up period of the present study, younger age at onset of cannabis use was associated with younger age at onset of the selected unspecific early and high-risk symptoms. This finding contributes to a growing awareness that cannabis use accelerates the development of psychotic-like symptoms. Further, it might add to their severity. Our findings might also contribute to a better understanding of the role cannabis use plays in the pathways to development of psychotic disorders. In clinical practice, young people with high-risk symptoms of course should be strongly advised against using cannabis. However, discouraging cannabis use in the UHR state may be a late stage of intervention. Universal primary preventive approaches to psychosis focusing on cannabis use in early adolescence as a potential risk factor might be a difficult but more promising strategy.

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