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# Cannabis use and vulnerability for psychosis in early adolescence—a TRAILS study

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## ABSTRACT

**Aims** To examine the direction of the longitudinal association between vulnerability for psychosis and cannabis use throughout adolescence. **Design** Cross-lagged path analysis was used to identify the temporal order of vulnerability for psychosis and cannabis use, while controlling for gender, family psychopathology, alcohol use and tobacco use. **Setting** A large prospective population study of Dutch adolescents [the TRacking Adolescents' Individual Lives Survey (TRAILS) study]. **Participants** A total of 2120 adolescents with assessments at (mean) age 13.6, age 16.3 and age 19.1. **Measurements** Vulnerability for psychosis at the three assessment points was represented by latent factors derived from scores on three scales of the Youth Self-Report and the Adult Self-Report, i.e. thought problems, social problems and attention problems. Participants self-reported on cannabis use during the past year at all three waves. **Findings** Significant associations ($r = 0.12$–$0.23$) were observed between psychosis vulnerability and cannabis use at all assessments. Also, cannabis use at age 16 predicted psychosis vulnerability at age 19 ($Z = 2.6$, $P < 0.05$). Furthermore, psychosis vulnerability at ages 13 ($Z = 2.0$, $P < 0.05$) and 16 ($Z = 3.0$, $P < 0.05$) predicted cannabis use at, respectively, ages 16 and 19. **Conclusions** Cannabis use predicts psychosis vulnerability in adolescents and vice versa, which suggests that there is a bidirectional causal association between the two.

**Keywords** Addictions, Adolescence, Bidirectional association, Cannabis, Drugs of Abuse, Vulnerability for Psychosis.

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## INTRODUCTION

Epidemiological research has provided extensive evidence of associations between cannabis use and psychosis [1–9]. Cannabis use has been associated with both subclinical psychotic experiences and clinical psychotic disorder. However, the direction of the (temporal) associations between cannabis use and psychotic symptoms has not yet been explained fully. Several hypotheses considering the direction of the effect have been proposed. There is evidence for a so-called 'self-medication hypothesis', where individuals are hypothesized to use cannabis in order to alleviate their psychotic symptoms or to improve their mood [10,11]. There is more evidence, however, supporting an association in the opposite direction. This is referred to as the damage hypothesis, where cannabis use causes or exacerbates psychotic symptoms (e.g. [3,5,7]). Finally, there are some longitudinal studies suggesting a bidirectional relationship between cannabis use and psychotic experiences or symptoms [7,12]. Neurobiological studies have suggested that cannabis can indeed induce psychotic experiences when excessive Δ-9-tetrahydrocannabinol ($\Delta^9$-THC-) stimulation of cannabinoid ($CB_1$-) receptors on gamma-aminobutyric acid (GABA)ergic and glutaminergic terminals causes disruptions in dopaminergic projections from the brain stem to the striatum [13,14]. It has also been proposed that the normally transient effects of $\Delta^9$-THC on physiological

control of the endogenous cannabinoid (CBD-) system over glutamate and GABA release may be more harmful during adolescence because of adverse effects on the ongoing rapid maturation of neural circuits (particularly prefrontal cortex) at that stage of life [15,16].

Studies into longitudinal cannabis–psychosis associations have often linked cannabis use during adolescence to psychotic experiences or symptoms in adulthood. Considering the rapid maturation of brain regions and neurotransmitter systems associated with both psychosis and cannabis exposure and subsequent increased vulnerability [15,16], however, it is important to focus additionally on the adolescent life phase itself when studying possible relationships. There are several other arguments for investigating the associations within adolescence itself. One is that psychosis proneness is often already evident during early adolescence, which may not be surprising considering its strong heritable component [17,18]. Although there may not yet be very obvious manifestations at this stage, there are proxy measures including specific cognitive, social and thought problems which appear to be good predictors of later subclinical or clinical psychosis [19–22]. Moreover, there is increasing evidence for stability or continuity (from adolescence onwards) of psychosis symptoms [23–25]. This parallels the continuity (and sometimes transition into addiction and/or use of heavier drugs) observed for cannabis use [26]. Further evidence supporting a focus on (early) adolescence itself stems from studies showing that those who initiated cannabis use earlier and/or used cannabis for longer periods of time carried a greater risk for schizophrenia outcomes and psychotic experiences than those who initiated cannabis use later and/or used cannabis for shorter periods of time [1,27–29]. Thus, in order to facilitate early recognition of psychosis (symptoms) and for a better understanding of the role of cannabis use in its development, research on their interrelations needs to incorporate important developmental stages including the entire period of adolescence.

The present study focused on the direction of temporal relationships between cannabis use and vulnerability for psychosis in a large population sample of adolescents ($n = 2120$) enrolled in the TRacking Adolescents' Individual Lives Survey (TRAILS) [30], controlling for possible confounding variables such as socio-economic status (SES), parental psychopathology and use of other substances. Assessment of both psychotic vulnerability and cannabis use at multiple time-points allowed testing of both the self-medication hypothesis and the damage hypothesis.

## METHOD

### Participants

Data were gathered from participants in the TRacking Adolescents' Individual Lives Survey (TRAILS), an ongoing prospective population study of Dutch adolescents investigated biennially until at least the age of 25 years.

The TRAILS target sample consisted of young adolescents from five municipalities in the north of the Netherlands, including both urban and rural areas. The sample selection involved two steps. First, the municipalities were requested to provide names and addresses of all inhabitants born between 10 January 1989 and 30 September 1990 (first two municipalities) or between 10 January 1990 and 30 September 1991 (last three municipalities), which yielded 3483 names. Simultaneously, primary schools (including schools for special education) within these municipalities were approached with a request to participate. School participation was a prerequisite for eligible adolescents and their parents to be approached by TRAILS, with the exception of adolescents who already attended secondary schools (<1%), who were contacted without involving their schools. Of the 135 primary schools within the municipalities, 122 (90.4%) schools agreed to participate, accommodating 90.3% of the adolescents.

Secondly, if schools agreed to participate, parents (or guardians) received two brochures, one for themselves and one for their adolescents, with information about the study. In addition, a TRAILS staff member visited the schools to inform eligible adolescents about the study.

More details about the procedure have been published elsewhere [30,31].

The exclusion criteria were: (i) adolescent's inability of participating because of intellectual disability or a serious physical illness or handicap; and (ii) Dutch-speaking parent or parent surrogate not available, and not feasible to administer a part of the measurements in the parent's own language. Of all subjects who were approached ($n = 3145$), 6.7% were excluded.

Of the remaining 2935 young adolescents, 76.0% were included in the study [T1: $n = 2230$, mean age: 11.1 years, standard deviation (SD): 0.6, 50.8% female]. For the present study, data from the first assessment (T1, mean age: 11.09 years; SD: 0.55; 50.8% girls) involved only control variables. Main analyses were performed with data of T2 (mean age: 13.6; SD: 0.5, 51% girls), T3, (mean age: 16.3 years; SD: 0.7, 52.3% girls) and T4, (mean age: 19.1; SD: 0.6, 52.3% girls), because there was no reporting on cannabis use at T1.

## MEASURES

### Cannabis use

Cannabis use by the participants was measured at the second, third and fourth assessments by self-report items on cannabis use in the last year with the following

 

questions: 'How often have you used cannabis in your life/in the last year', with answer categories: 'I have never used', 'used it once', 'used it twice', 'three times', . . . , '10 times', '11–19 times', '20–39' times, '40 times or more'. Items were recoded into four categories; (i) no use; (ii) one to two times during the past year, (iii) three to six times during the past year; and (iv) seven times or more during the past year.

Other studies focusing on cannabis use have recoded the above answer possibilities into the following categories: (i) those who had never used; (ii) those who had used but not during the past year, (discontinued use); (iii) those who used once or twice during the past year, (experimental use); (iv) those who reported using cannabis between three and 39 times during the past year, (regular use); and (v) those who reported using it 40 times or more during the last year (heavy use) [32,33]. Whereas it is more customary to use these categories, cross-lagged path analysis requires linear variables. The more traditional categorization did not result in a linear variable or a variable that could be used as such. In order to obtain a variable/categorization that best approached linearity, Tukey's transformation ladder was used [34]. According to Tukey, a variable can be interpreted as linear (with equal distances between categories) when a straight line results after plotting the logarithmic transformation of the variable against the raw data. Using categories no use (i), one to two times (ii), three to six times (iii) and seven times or more (v) resulted in the best Tukey solutions for T2, T3 and T4.

### Psychosis vulnerability

Psychosis vulnerability was conceptualized as a latent factor, indicated by three subscales of the Youth Self-Report (YSR) at measurement waves T2 and T3, and the Adult Self-Report (ASR) at T4; the thought problems, attention problems and social problems scales. The YSR is one of the most commonly used self-report questionnaires in current child and adolescent psychiatric research, and is appropriate for ages 11–19 [35,36]. The YSR contains 112 items on behavioural and emotional problems in the past 6 months that can be rated as being not true (0), somewhat or sometimes true (1), or very or often true (2). The ASR is the equivalent of the YSR for individuals aged 18–59, and includes many of the YSR items, including some extra items on transitions to adulthood [35]. Attention problems of both the YSR and the ASR include items such as 'having trouble concentrating'. The thought problems scales of the YSR and the ASR include 12 items such as 'seeing things that other people do not see'. Following earlier work [24], three items (on skin picking; storing up many things and sleeping less than other children) were excluded based on their low Spearman's inter-item correlations with the other items, leaving nine items in this subscale. For consistency, these items were also excluded from the ASR.

The social problems scale of the YSR includes 11 items such as 'feeling lonely' and 'not getting along with other boys and girls'. As only seven of the original 11 items of the social problems scale of the ASR were measured at T4, we have converted all measures of the YSR and ASR into Z-scores in further analyses to account for potential biases. Internal consistency for all subscales of YSR and ASR, measured at T2-3-4, was acceptable (Cronbach's $\alpha$ ranged between 0.62 and 0.84).

### Control variables

#### *Use of other substances*

Tobacco use was measured at T2, T3 and T4, where adolescents were asked about their use in the last month. Answers were recoded into non-weekly versus weekly tobacco use. Use of alcohol was also measured at T2, T3 and T4, where adolescents were asked about the frequency of alcohol use in the past month. Alcohol use was recoded into non-monthly versus monthly use. These categories (for both tobacco use and alcohol use) were similar to those used in other studies focusing on cannabis use and mental health (e.g. [33]).

#### *Socioeconomic status (SES)*

SES was assessed at baseline (T1) using a five-point scale consisting of five variables: educational level (father/mother), occupation (father/mother) and family income. The internal consistency of this measure is good (Cronbach's alpha 0.84) [37].

#### *Parental psychopathology*

Parental psychopathology (i.e. depression, anxiety, substance abuse, antisocial behaviour and psychosis) was measured by means of the brief TRAILS family history interview [37,38], administered at baseline (T1). The scores for substance abuse and antisocial behaviour were used to construct a familial vulnerability index for externalizing disorder. The scores for depression and anxiety disorder were used to construct an index for internalizing disorder. More information on the construction of familial vulnerability within TRAILS can be found elsewhere [37,38].

### Data analysis

Around 50% of the original sample ($n = 1123$) had complete data on all variables of interest measured at various waves. Consequently, the results of 'complete-case' analyses could potentially be biased. Using the method of

**Table 1** Descriptive information on cannabis use during the past year T2, T3 and T4 ($n = 2120$).

| | *T2* | *T3* | *T4* |
|---|---|---|---|
| No use | 94.2% ($n = 1997$) | 74.2% ($n = 1574$) | 65.3% ($n = 1385$) |
| 1–2 times | 3.0% ($n = 63$) | 7.6% ($n = 162$) | 10.7% ($n = 227$) |
| 3–6 times | 1.5% ($n = 32$) | 7.4% ($n = 157$) | 8.1% ($n = 171$) |
| 7 times or more | 1.3% ($n = 28$) | 10.7% ($n = 227$) | 15.8% ($n = 336$) |

multiple imputation [39,40], where multiple versions of the data set are produced, each containing its own set of imputed values, and parameter estimates for all imputed data sets are pooled for further statistical analyses, missing data at T2, T3 and T4 were imputed. First, participants missing data on either 'cannabis use' or 'psychosis vulnerability' at all three waves were deleted from the sample ($n = 110$), before imputation was carried out. Fully conditional specification (FCS), an iterative Markov chain Monte Carlo (MCMC) method, which for each variable in the order specified in the variable list fits a univariate model using all other available variables in the model as predictors, was chosen for multiple imputation. Data from T1 were entered only as 'predictor variables' of missing data of T2, T3 and T4. These included SES, gender, parental psychopathology and YSR scales of social problems, attentional problems and thought problems. All the above-mentioned variables plus cannabis use from T2, T3 and T4 were included in the model as both predictors and imputed data.

In order to determine which variables should be included in the main analyses as covariates, it was examined whether there were differences between cannabis users (those indicating having used cannabis at least once) and non-users with respect to SES, parental psychopathology, use of alcohol and tobacco and gender.

The temporal order of occurrence of cannabis use and psychosis vulnerability was investigated using path analyses. Following the two-step approach recommended by Anderson & Gerbin [41], confirmatory factor analysis (CFA) was used first to investigate how well our hypothesized models fit the actual data. The models were based on the notion that either vulnerability for psychosis predicted cannabis use or the other way around.

Next, cannabis use and vulnerability for psychosis, identified in the CFA, were modelled prospectively. Here, we included all possible associations between latent variables and all significant control variables. To evaluate the overall model fit, the root mean square error of approximation was used (RMSEA) [42]; a RMSEA value less than 0.05 indicates good model fit [43]. Both $\chi^2$ statistics and RMSEA are dependent on the size of the sample: as we had a relatively large sample ($n = 2120$), we also used the comparative fit index (CFI) [44] to evaluate overall model fit. A CFI value greater than 0.90 indicates good model fit [43]. All analyses were performed using EQS version 6.1 for Windows [45].

## RESULTS

### Preliminary analysis

Cannabis users ($n = 940$) did not differ from non-users ($n = 1180$) with respect to familial vulnerability for internalizing disorders [$t_{(2118)} = -1.8$, $P = 0.066$]. Cannabis users were more often boys than girls (54.9 versus 43.6%; $\chi^2_{(1)} = 26.9$, $P < 0.001$), monthly alcohol users (54.0% versus 29.2%; $\chi^2_{(1)} = 133.9$, $P < 0.001$ at T2; 89.5% versus 68.2%; $\chi^2_{(1)} = 136.1$, $P < 0.001$ at T3; 94.3% versus 77.8%; $\chi^2_{(1)} = 110.9$, $P < 0.001$ at T4) and weekly tobacco users (16.2% versus 3.1%; $\chi^2_{(1)} = 109.5$, $P < 0.001$ at T2; 57.9% versus 18.0%; $\chi^2_{(1)} = 363.2$, $P < 0.001$ at T3; 54.0% versus 29.2%; $\chi^2_{(1)} = 133.9$, $P < 0.001$ at T4). Furthermore, cannabis users and non-users differed significantly with respect to SES ($t_{(2118)} = -3.0$ $P = 0.002$) and familial vulnerability for externalizing disorders ($t_{(2118)} = -2.3$, $P = 0.022$), where cannabis users scored higher on familial vulnerability for externalizing disorders and SES than non-users. Of these variables, SES was not related to indicators of psychosis vulnerability and therefore not introduced as a covariate. Gender, familial vulnerability for externalizing disorders, alcohol use and tobacco use were related to psychosis vulnerability and therefore included as covariates in subsequent path analyses.

### Descriptives

Descriptive information regarding the frequency of cannabis use is presented in Table 1.

### Path analysis; preliminary analysis (CFA)

The independent model which tested the hypothesis that all cannabis scores and psychosis vulnerability were uncorrelated was rejected: $\chi^2_{(1)(33, n = 2120)} = 207.1$, $P \leq 0.001$; RMSEA = 0.05; CFI = 0.98. The model provided an acceptable fit to the data. Table 2 shows the correlations between all latent variables. All correlations

 

**Table 2** Correlations between cannabis use and the latent variables for psychosis vulnerability from the confirmatory factor analysis ($n = 2120$).

| | *T2 Cannabis use* | *T3 Cannabis use* | *T4 Cannabis use* |
|---|---|---|---|
| T2 Vulnerability for psychosis | 0.12* | 0.15* | 0.12* |
| T3 Vulnerability for psychosis | 0.08* | 0.17* | 0.15* |
| T4 Vulnerability for psychosis | 0.07* | 0.17* | 0.23* |

*$P < 0.05$.

between psychosis vulnerability and cannabis use were significant ($P \leq 0.05$). Also, correlations became stronger over time.

### Cannabis use and psychosis vulnerability

Next, we performed a path analysis to address the temporal order of cannabis use and psychosis vulnerability, after including the following covariates: gender, familial vulnerability for externalizing disorders, alcohol (T2-3-4) and tobacco use (T2-3-4). Figure 1 presents details on the path analysis of psychosis vulnerability and cannabis use, including factor loadings and correlations.

The model represented the data well $\chi^2_{(146, n=2120)} = 1214{,}5$, $P < 0.001$; RMSEA = 0.06, CFI = 0.92. As expected, the stability paths between vulnerability for psychosis measured at T2, T3 and T4 were all significant (T2–T3; $Z = 22.6$, $P < 0.05$ and T3–T4; $Z = 23.8$, $P < 0.05$) and so were the stability paths for cannabis use at the three different assessment points (T2–T3; $Z = 8.1$, $P < 0.05$ and T3–T4; $Z = 20.6$, $P < 0.05$).Vulnerability for psychosis at T2 predicted cannabis use at T3 ($Z = 2.0$, $P < 0.05$). Similarly, vulnerability for psychosis at T3 predicted cannabis use at T4 ($Z = 3.0$, $P < 0.05$). Also, cannabis use measured at T3 significantly predicted psychosis vulnerability measured at T4 ($Z = 2.6$, $P < 0.05$). Lastly, cannabis use measured at T2 did not predict psychosis vulnerability measured at T3 ($Z = 0.3$, $P > 0.05$).

## DISCUSSION

This study investigated the longitudinal and bidirectional relationship between cannabis use and vulnerability for psychosis, as indicated by thought problems, social problems and attention problems, in a sample of 2120 adolescents from the Dutch general population. The directionality of the longitudinal association between cannabis use and vulnerability for psychosis was examined by testing two contrasting hypotheses, the damage hypothesis and the self-medication hypothesis, using path analyses and controlling for possible confounding factors.

The results showed that throughout adolescence, vulnerability for psychosis was associated with cannabis use. When investigating the temporal order of this relationship, bidirectional associations became apparent. More specifically, cannabis use at age 16 predicted vulnerability for psychosis at age 19, but psychosis vulnerability at age 16 also predicted cannabis use at age 19. Moreover, psychosis vulnerability at age 13 predicted cannabis use at age 16. Cannabis use at age 13 did not predict vulnerability for psychosis at age 16, but this could be due to a lack of statistical power, as the number of adolescents that had actually used cannabis at T2 was quite small ($n = 123$).

It may be concluded that the results provide empirical support for both the damage and the self-medication hypothesis. Whereas evidence has been provided for apparent unidirectional associations in many earlier studies (e.g. [1–12]), not many studies have been able to include multiple measurement points and thus test bidirectional associations. Moreover, some very plausible explanations have been offered for why the temporal association would head one way or the other. With respect to self-medication, it has been hypothesized specifically that individuals with psychosis symptoms use cannabis to improve their mood or to control one's feelings, boredom, social motives, improving sleep, anxiety and agitation, although some studies indicate that individuals with psychosis symptoms use cannabis for similar reasons as the general population as well, i.e. 'to get high', relax and have fun [10,11,46]. With respect to the damage hypothesis, there is support from neurobiological studies, which also indicate adolescence as a particularly vulnerable period for the effects of cannabis. However, when studies have been able to include multiple measurement points, the existence of bidirectional associations generally becomes evident [12]. The results of the present study give rise to the thought that a cascading model would fit the temporal associations between cannabis use and psychosis vulnerability best, particularly because associations between cannabis use and psychosis vulnerability became stronger at later assessments. In order to be able to study this in more detail, different statistical approaches might have to be chosen and possible moderation effects should also be taken into account. There are several studies showing interactions between particular gene variants, as well as environmental factors and cannabis use in the prediction of psychosis [47–50].

Some limitations of the present study should be kept in mind when interpreting the results. First, data of the present study are all based on self-report. Although clinical interviews for assessment of psychosis vulnerability and multiple informants would have been preferable, previous studies have concluded that both substance use behavior and mild psychotic symptoms can be investi-

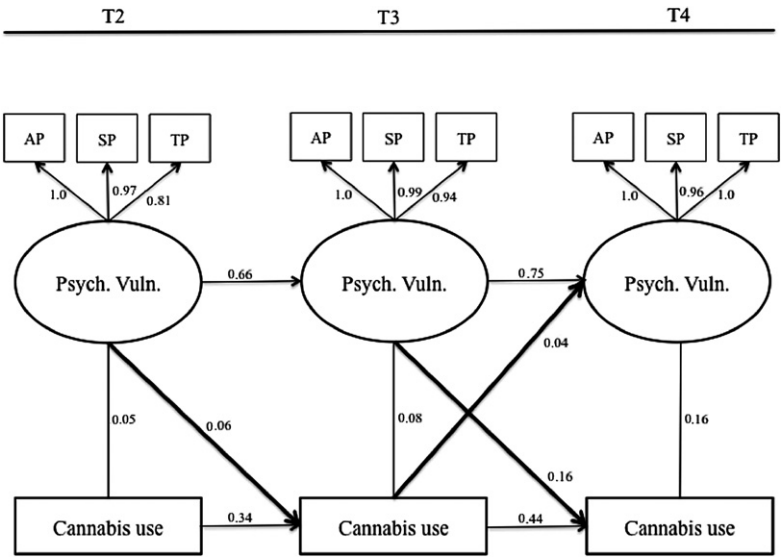


**Figure 1** Path analysis of psychosis vulnerability (Psych.Vuln.), with indicators: thought problems (TP), social problems (SP) and attention problems (AP) and cannabis use during adolescence after controlling for gender, parental psychopathology, tobacco (T2-3-4) and alcohol use (T2-3-4) ($n = 2120$). All non-significant paths have been removed from the full model. Latent variables are shown in ellipses, and observed variables are shown in rectangles

gated reliably by self-report [51]. Another limitation is that, despite the fact that several important potential confounders have been taken into account, we cannot claim to have been all-inclusive in this respect. Whereas this would be the case for most, if not all large cohort studies, it may be argued that the choice of potential confounders could have been more refined. For example, the genetic variation associated with psychosis vulnerability and substance use could manifest itself in (impairments in) certain (dopamine or serotonin-dependent) cognitive abilities that could have been assessed as well. A third possible limitation is that three scales of the Youth Self-Report and Adult Self-Report were used as indicators of psychosis vulnerability. Although these scales were shown to be associated with psychosis [19–22], and may be good indicators of early manifestations of psychosis that could develop into the clinical disorder, future studies may also want to include instruments measuring psychosis symptoms more directly [52].

The strengths of the current study include its longitudinal design, which allowed for investigation of the bidirectional relationship between cannabis use and vulnerability for psychosis. Secondly, the starting point of the TRAILS study is early adolescence, which allowed investigation of (factors associated with) cannabis use and development of psychosis from an earlier and possibly more crucial age compared to most other studies. This is particularly important considering recent hypotheses stating that cannabis-induced psychosis may be a distortion of normal adolescent brain maturation [15]. Thirdly, a number of important control variables were included in the analyses, including the use of other substances and parental psychopathology.

In conclusion, the present study showed that cannabis use at age 16 predicted psychosis vulnerability at age 19, and psychosis vulnerability at age 13 and 16 predicted cannabis use at, respectively, age 16 and 19, thereby providing evidence for both the damage hypothesis and self-medication hypotheses. Prevention programmes aimed at delaying and preventing transition from subclinical psychotic symptoms to clinical disorder should target the entire adolescent life phase and pay attention to cannabis use at this period in time.

## Declarations of interest

Frank Verhulst is publisher of the Dutch translation of ASEBA materials, from which he receives enumeration. All other authors declare no conflicts of interest.

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