

Association Between Cannabis Use and Psychosis-Related Outcomes Using Sibling Pair Analysis in a Cohort of Young Adults

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ABSTRACT

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Context Prospective cohort studies have identified an association between cannabis use and later psychosis-related outcomes, but concerns remain about unmeasured confounding variables. The use of sibling pair analysis reduces the influence of unmeasured residual confounding.

Objective To explore the association between cannabis use and psychosis-related outcomes.

Design A sibling pair analysis nested within a prospective birth cohort.

Setting Births at a Brisbane, Australia, hospital.

Participants Three thousand eight hundred one young adults born between 1981 and 1984 as part of the Mater-University Study of Pregnancy.

Main Outcome Measures Cannabis use and 3 psychosis-related outcomes (nonaffective psychosis, hallucinations, and Peters et al Delusions Inventory score) were assessed at the 21-year follow-up. Associations between duration since first cannabis use and psychosis-related outcomes were examined using logistic regression adjusted for sex, age, parental mental illness, and hallucinations at the 14-year follow-up. Within 228 sibling pairs, the association between within-pair differences in duration since first cannabis use and Peters et al Delusions Inventory score was examined with general linear modeling. The potential impact of attrition was examined.

Results Duration since first cannabis use was associated with all 3 psychosis-related outcomes. For those with duration since first cannabis use of 6 or more years, there was a significantly increased risk of (1) nonaffective psychosis (adjusted odds ratio, 2.2; 95% confidence interval, 1.1-4.5), (2) being in the highest quartile of Peters et al Delusions Inventory score (adjusted odds ratio, 4.2; 95% confidence interval, 4.2-5.8), and (3) hallucinations (adjusted odds ratio, 2.8; 95% confidence interval, 1.9-4.1). Within sibling pairs, duration since first cannabis use and higher scores on the Peters et al Delusions Inventory remained significantly associated.

Conclusions Early cannabis use is associated with psychosis-related outcomes in young adults. The use of sibling pairs reduces the likelihood that unmeasured confounding explains these findings. This study provides further support for the hypothesis that early cannabis use is a risk-modifying factor for psychosis-related outcomes in young adults.

INTRODUCTION

Prospective cohort studies have found that early-onset cannabis use is associated with an increased risk of psychosis-related outcomes.¹⁻⁷ Based on these studies and a range of other lines of evidence, reviews have generally concluded that cannabis use is a risk-modifying factor for these outcomes (ie, cannabis use is causally related to psychosis-related outcomes).⁸⁻¹³ However, there are lingering concerns that the association may reflect methodological biases and unmeasured residual confounding.¹⁴⁻¹⁵ In a recent meta-analysis, Moore and colleagues¹¹ noted that after adjusting for various methodological issues, there were often substantial reductions in the effect size between cannabis use and later psychosis-related outcomes. Because the pooled effect size reported by Moore and colleagues was modest (adjusted odds ratio, 1.41; 95% confidence interval [CI], 1.20-1.65), the role of residual confounding cannot be discounted. In light of the limitations of observational epidemiology,¹⁶ it is understandable that there is debate about the public health implications of these findings.^{15, 17}

Despite the oft-repeated concerns about the role of residual confounding, the research community has yet to explore the association between cannabis and psychosis outcomes using sibling pair designs. Twin and other sibling pair studies provide a quasi-experimental design that can help address the issue of residual confounding. Sibling pair designs capitalize on between-sibling differences while reducing the influence of unmeasured confounding factors, since differences are

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less likely to be attributable to shared genetic and environmental exposures. Twin studies have explored cannabis use as a "gateway" to other illicit drug use,¹⁸ but, to our knowledge, no study has used a sibling pair design to examine the association between cannabis use and psychosis-related outcomes. If a significant association between cannabis use and psychosis-related outcomes was not detected in sibling pairs, it would seriously weaken the argument that cannabis use was a risk-modifying factor for psychosis-related outcomes. The aims of this study were to explore the association between cannabis use and multiple psychosis-related outcomes in a birth cohort and to further examine if these associations persisted within nested sibling pairs.

METHODS

PARTICIPANTS

The Mater-University Study of Pregnancy, and its outcomes, is a prospective study of 7223 women and their singleton offspring who received antenatal care at a major public hospital in Brisbane, Australia, between 1981 and 1984. The cohort members (and their mothers) were followed up at 5, 14, and 21 years (eFigure 1). Of the original sample, follow-up responses were obtained for 3801 children (53%) at the 21-year follow-up. Full details of the Mater-University Study of Pregnancy study design, sampling strategy, attrition, and follow-up sample characteristics are available elsewhere.¹⁹

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MEASUREMENT OF MAIN EXPOSURES

At the 21-year follow-up, cannabis use was retrospectively assessed via a self-report questionnaire. Cohort members were asked "In the last month, how often did you use cannabis, marijuana, pot, etc?" Options for response were have never used, used every day, every few days, once or so, and not in the last month. A second question sought the age at which use of cannabis began. Based on these variables, and the cohort members' age at interview, we derived a measure of duration since first cannabis use. This variable was categorized into 4 levels, with those who had never used cannabis in 1 group (the reference group) and those who had used cannabis divided into 3 approximately equal groups (≤ 3 years, 4 or 5 years, ≥ 6 years). Because members of this birth cohort were assessed within a relatively narrow age range, longer duration since first cannabis use is equivalent to an earlier age at first cannabis use.

To explore the validity of this item, we examined the association between duration since first cannabis use (a retrospective measure) vs a prospective measure of alcohol and illicit drug use that was assessed at the 14-year follow-up as part of the widely used Youth Self-Report²⁰ ("I use alcohol and drugs for nonmedicinal purposes").

MEASUREMENT OF OUTCOME VARIABLES

We examined 3 psychosis-related outcomes. At the 21-year follow-up, 2575 of the 3801 cohort members were administered the computerized lifetime version of the Composite International Diagnostic Interview (CIDI).²¹ Not all cohort members received the CIDI, but this was because of insufficient funding rather

than any systematic bias (see later for analyses related to missing values). For the current study, we defined "caseness" as having an *International Statistical Classification of Diseases, 10th Revision (ICD-10)*²² diagnosis of nonaffective psychosis based on meeting the criteria for the diagnoses of either schizophrenia (*ICD-10* code F20), persistent delusional disorder (*ICD-10* code F22), or acute and transient psychotic disorders (*ICD-10* code F23). We also examined the 21-item version of the Peters et al Delusions Inventory (PDI), an instrument used to measure delusional-like experiences in clinical and community populations.²³⁻²⁴ Finally, we examined 2 specific CIDI items designed to assess the presence of auditory and visual hallucinations. Cohort members were grouped into those who endorsed no hallucination items vs 1 or more.

MEASUREMENT OF POTENTIAL CONFOUNDERS AND OTHER EXPLANATORY FACTORS

It is feasible that early psychotic-like experiences could influence both subsequent cannabis use and psychosis-related outcomes at the 21-year follow-up. At the 14-year follow-up, 2 items from the Youth Self-Report²⁰ were chosen for their face validity as psychotic-like experiences: "I hear sounds or voices that other people think aren't there" and "I see things that other people think aren't there." Based on this same cohort, we previously reported that these items were associated with both an increased risk of nonaffective psychosis²⁵ and high scores on the PDI²⁶ at the 21-year follow-up. Subjects were dichotomized into those who responded "never" vs "sometimes" or "often."

Parental mental illness is a potential confounding factor because this could influence both the risk of cannabis use and psychotic-related outcomes in the offspring.²⁷⁻³⁰ At the 5, 14, and 21-year follow-ups, mothers of the cohort members were asked to report on specific parental mental illnesses (maternal or paternal history of schizophrenia, alcohol abuse/dependence, and depression or anxiety disorders). Subjects were dichotomized into parental history of mental disorder present or absent.

MAIN AND PLANNED SENSITIVITY ANALYSES

We used maximum likelihood logistic regression to examine the associations between duration since first cannabis use and each of the 3 main outcomes variables in separate analyses (ie, nonaffective psychosis, PDI total score, and the CIDI hallucination items). In keeping with previous analyses,²⁶ the total score of the PDI was divided into quartiles. For model 1, the analyses were adjusted for sex and age of the cohort members at the 21-year follow-up (age at testing varied slightly at each follow-up). For model 2, we also included adjustments for 2 additional variables: (1) parental mental illness and (2) hallucinations at age 14 years as assessed on the Youth Self-Report.

Several planned sensitivity analyses were undertaken. For the assessment of the PDI total score and CIDI hallucination items, we conducted the analyses again excluding cohort members who (1) received a CIDI-derived diagnosis of nonaffective psychosis (to examine psychotic-like experiences in the cohort members without diagnostic-level psychotic disorders) or (2) reported any cannabis use in the month prior to the 21-year follow-up interview (to reduce the potential influence of acute intoxication or withdrawal on the outcome measures). Cannabis use has also been associated with later depression and anxiety.¹¹ Using the major CIDI-derived diagnoses of depression (*ICD-10* codes F32, F33, and F34) and anxiety disorders (*ICD-10* codes F40, F41, and F43), we examined the association between duration since first cannabis use and the

psychosis-related outcomes in models that adjusted for the presence of these disorders. To focus on issues related to reverse causality, we also examined the association between endorsement of hallucination items at age 14 years on the Youth Self-Report and both frequency of cannabis use and duration since first cannabis use (assessed at the 21-year follow-up), excluding those who used cannabis before age 15 years.

SIBLING PAIR ANALYSIS

While the Mater-University Study of Pregnancy cohort was restricted to singleton offspring, during the period of recruitment several hundred sibling pairs were recruited into the study (there were no sibships with greater than 2 members included in the cohort). We identified 228 sibling pairs who participated in the 21-year follow-up and who provided information on the variables of interest (60 male sibling pairs, 65 female sibling pairs, and 103 mixed-sex sibling pairs). The maximum between-sibling age difference was 4 years, with 92% of the siblings differing in age by 3 years or less. Eighty-three percent of the mothers of the sibling pairs reported no change in partners over the period of the birth of the 2 siblings.

Following methods outlined elsewhere,³¹⁻³² an index sibling was randomly selected, and difference scores between the siblings for (1) years since first cannabis use and (2) PDI total score were generated (index sibling minus other sibling). For example, within a sibling pair, if (1) the index sibling had 6 years since first cannabis use and a PDI total score of 10 items while (2) the other sibling had 2 years since first cannabis use and a PDI total score of 3 items, then (3) the years since first cannabis use difference score would be 4 years and the PDI difference score would be 7 items. For each sibling pair, the association between years since first cannabis use difference score (the predictor variable) vs the PDI difference score (the outcome variable) was examined, when adjusted for differences in sibling age and sex. Sibling pairs that included a cohort member with an *ICD-10* diagnosis of nonaffective psychosis were excluded from the main analysis.

It could be argued that siblings discordant for cannabis use (ie, one sibling who had never used cannabis and a sibling who had used cannabis for several years) may differ in a range of factors that could impact both the exposure variables (ie, propensity to use illicit drugs) and subsequent mental health. Thus, we undertook an additional planned sensitivity analysis where we restricted the sibling pairs to those who both used cannabis. This analysis allowed an even greater focus on the critical nonshared exposure (ie, duration since first cannabis use) and the psychosis-related outcomes.

POTENTIAL IMPACT OF MISSING DATA AND ATTRITION

We explored the influence of attrition using 2 methods. First, we used SAS Proc MI and MIanalyze (SAS Institute Inc, Cary, North Carolina) to explore the data under the assumption that data were missing randomly. For the multiple imputation, we included the variables of interest used in the earlier-mentioned models and also variables known to be associated with attrition in this cohort (ie, birth weight and various maternal variables at first clinic visit related to age, education, marital status, mental health, and smoking).¹⁹ We used logistic regression based on 20 imputed data sets. Finally, based on the assumption that the data were missing in a nonrandom fashion, we undertook a post hoc modeling exercise to explore the robustness of the main findings under a set of assumptions that would be potentially challenging to these findings.

Analyses were performed using SAS version 9.1 (SAS Institute Inc). Written informed consent was obtained from the mother at all data collection phases and from the young adult at the 21-year follow-up. Ethical approval for this study was obtained from the University of Queensland Ethics Committee.

RESULTS

In total, 3801 subjects (1806 males) were included in the analyses, with mean (SD) age of 20.1 (0.90) years (range, 18 to 23 years). Overall, 65 subjects received a diagnosis of nonaffective psychosis (*ICD-10* code F20 schizophrenia, $n = 53$; *ICD-10* code F22 persistent delusional disorder, $n = 3$; and *ICD-10* code F23 acute and transient psychotic disorders, $n = 9$), while 233 endorsed at least 1 CIDI hallucination item. The total PDI score ranged from zero to 21 endorsed items (mean [SD], 5.1 [3.6] items; median, 4.0 items). The quartiles for the PDI total score divided the subjects into (1) 2 or less, (2) 3 or 4, (3) between 5 and 7, and (4) 8 and more items. The association between a range of demographic and potential confounding variables is shown in [Table 1](#). In keeping with previous analyses, sex, age at testing, parental mental illness, and hallucinations at age 14 years were significantly associated with some or all of the psychosis-related outcomes.

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Table 1. Psychosis-Related Outcomes at the 21-Year Follow-up by Demographic and Covariate Factors

At the 14-year follow-up, 283 cohort members (7.9%) reported using alcohol or illicit drugs. At the 21-year follow-up, 17.7% reported using cannabis for 3 or fewer years, 16.2% for 4 to 5 years, and 14.3% used for 6 or more years. Among those who had ever used, 52.6% had not used in the previous month, 11.0% reported daily use, 13.8% reported use "every few days," and 22.6% reported use "once or so per month." With respect to the validity of the main exposure measure, there was a significant and strong relationship between the prospective assessment of alcohol or illicit drug use at the 14-year follow-up and longer duration since first cannabis use at the 21-year follow-up (Wald test = 231; $df = 3$; $P < .001$). Those who reported alcohol or illicit drug use at the 14-year follow-up were 15 times more likely to subsequently report 6 years' or more duration since first cannabis use (odds ratio, 14.7; 95% CI, 10.2-21.2).

[Tables 2](#), [3](#), and [4](#) show the association between duration since first cannabis use and the 3 psychosis-related outcome measures. Only those with the longest duration since first cannabis use were at significantly increased risk of nonaffective psychosis: those with 6 or more years duration since first cannabis use (ie, use since around 15 years of age) were twice as likely to receive a diagnosis of nonaffective psychosis.

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Table 2. Association Between Duration Since First Cannabis Use and Nonaffective Psychosis at the 21-Year Follow-up

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Table 3. Association Between Duration Since First Cannabis Use and PDI Total Score Quartiles

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Table 4. Association Between Duration Since First Cannabis Use and the Presence of Hallucinations at the 21-Year Follow-up

In [Table 3](#), only the highest vs lowest PDI total score quartile odds ratios are shown. Compared with those who did not use cannabis, cannabis users were significantly more likely to be in the highest quartile of the PDI scores. Those with a duration since first cannabis use of 6 or more years were 4 times more likely to be in the top PDI score quartile and twice as likely to endorse CIDI hallucination items ([Table 4](#)). There were significant linear trends between the exposure variable and all 3 psychosis-related measures: the longer the duration since first cannabis use, the higher the risk of the adverse outcomes.

For the PDI score and hallucination outcomes, we conducted a sensitivity analysis excluding individuals with nonaffective psychosis and those who had used cannabis in the month prior to the 21-year follow-up ([eTable 1](#)). The association between years since first cannabis use and PDI total score remained significant for those who had 4 years or more since first cannabis use. With respect to CIDI hallucination items, only those who had 4 or 5 years since first cannabis use had a significantly increased risk of reporting hallucinations at age 21 years. When we made additional adjustments to the model to include the presence of a depressive or anxiety disorder ([eTable 2](#)), the point estimates for all 3 analyses dropped slightly and the CIs became more imprecise, suggesting that these factors influenced the associations of interest. Only the analyses related to years since first cannabis use and (1) PDI total scores and (2) hallucinations remained statistically significant.

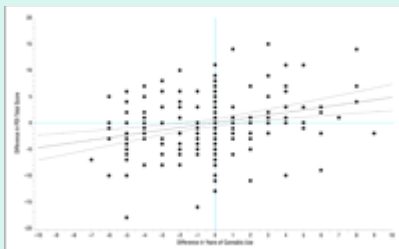
With respect to the potential for reverse causality, we found that hallucinations

at the 14-year follow-up were significantly associated with longer duration since first cannabis use by the 21-year follow-up (Table 5). Furthermore, compared with those who did not report hallucinations, those with hallucinations at the 14-year follow-up were twice as likely to be using cannabis on a daily basis at the 21-year follow-up (model 1, adjusted odds ratio, 2.1; 95% CI, 1.4-2.9).

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Table 5. Association Between Hallucinations at 14-Year Follow-up and Duration Since First Cannabis Use Assessed at 21-Year Follow-up^a

Within the sibling pair sample, there were 10 pairs who were discordant for nonaffective psychosis (there were no pairs concordant for nonaffective psychosis at the 21-year follow-up). For the discordant sibling pairs, we calculated the difference in years since first cannabis use for the affected minus the nonaffected sibling. The median difference was 1.5 years (mean [SD], 0.4 [3.3] years, range, -6 to 4 years). However, within this small sample, there was no significant difference in years since first cannabis use between the affected vs nonaffected siblings when adjusted for age and sex ($F_{1,5} = 0.60$; $P = .49$). Concerning the main analysis, within the nonaffected sibling pairs (sib pairs = 218), there was a significant association between years since first cannabis use and PDI total difference scores when adjusted for differences in age and sex ($F_{1,213} = 18.5$; $P < .001$). Compared with their sibling, those with more years since first cannabis use were more likely to have higher PDI total scores. The model (which explained 19% of the variance) found that for every additional year since first exposure to cannabis, the sibling with the earlier age at first use had scored approximately 1 PDI item higher compared with their sibling (per annum increase in PDI total score = 0.8; 95% CI, 0.7-0.9). The Figure shows a scatterplot with each point representing 1 sibling pair. When sibling pairs were restricted to those where both siblings had used cannabis (100 sibling pairs), the significant relationship between years of cannabis use and PDI scores persisted ($F_{1,95} = 6.4$; $P = .01$) (eFigure 2).



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Figure. Sibling pair analysis. Correlation between within-pair difference in years of cannabis use vs difference in Peters et al Delusions Inventory (PDI) total score. Each dot represents 1 sibling pair. Negative values indicate that the index sibling had lower values on the variable of interest compared with his or her sibling. Vertical and horizontal blue lines represent zero (ie, no difference between the siblings). The solid line is the regression and the dotted lines

show the 95% confidence intervals (based on mean values).

The association between years since first cannabis use and PDI total score was reexamined using imputed missing data (eTable 3). The significant findings persisted and the point estimates and CIs remained essentially unchanged. Finally, we modeled a conservative missing data scenario where we assumed that (1) all subjects with missing data on years since first cannabis use were users and randomly allocated them between 1 to 8 years' duration since first cannabis use and (2) those with missing values were more likely to have lower PDI total scores (to challenge our main empirical finding) and randomly allocated these subjects to the lower 2 PDI score quartiles. The resulting effect sizes for model 2 fell sharply, but compared with those who never used cannabis, the association between 6 or more years' duration since first cannabis use and higher PDI total scores remained statistically significant.

COMMENT

Longer duration since first cannabis use was associated with multiple psychosis-related outcomes in young adults. Furthermore, we report for the first time, to our knowledge, that this association persisted when examined in sibling pairs, thus reducing the likelihood that the association was due to unmeasured shared genetic and/or environmental influences. There was a "dose-response" relationship between the variables of interest: the longer the duration since first cannabis use, the higher the risk of psychosis-related outcomes. The key findings were robust in the face of various planned sensitivity analyses and conservative tests related to attrition.

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Compared with those who had never used cannabis, young adults who had 6 or more years since first use of cannabis (ie, who commenced use when around 15 years or younger) were twice as likely to develop a nonaffective psychosis and were 4 times as likely to have high scores on the PDI. Further analyses demonstrated that these findings were not due to a small group of individuals with psychotic disorders nor to individuals who were acutely intoxicated with cannabis when completing the PDI.

Sibling pair analysis provides the opportunity to control for a range of unmeasured potential confounding variables. We identified a small but significant positive association between years since first cannabis use and scores on the well-validated measures of delusional-like experiences. Reassuringly, this association persisted when we restricted the analysis to sibling pairs concordant for any cannabis use. This more stringent analysis provided a sharper focus on the critical nonshared exposure (ie, duration since first cannabis use).

With respect to genetic background, the cohort members within the sibling pairs shared the same mother, and the majority (we assume) shared the same father. Because of the age proximity of the siblings, we can also feel confident that a range of family milieu and socioeconomic factors remained reasonably constant

for the sibling pairs during early childhood. Of course, a range of exposures would still differ between the siblings (eg, the use of alcohol and illicit substances), and we would expect these nonshared exposures to become more prominent with age (eg, after the cohort members left the family home).

The nature of the relationship between psychosis and cannabis use is by no means simple. In keeping with previous findings,³³ we confirmed that those with early-onset hallucinations were more likely to have longer duration since first cannabis use and to use cannabis more frequently at the 21-year follow-up. This demonstrates the complexity of the relationship: those individuals who were vulnerable to psychosis (ie, those who had isolated psychotic symptoms) were more likely to commence cannabis use, which could then subsequently contribute to an increased risk of conversion to a nonaffective psychotic disorder. In addition, analyses that incorporated adjustments for depressive and anxiety-related disorders led to a reduction in the strength of the association between cannabis use and psychosis-related outcomes. This suggests that depression and/or anxiety disorders may mediate or moderate the pathways between cannabis use and psychosis-related outcomes. We plan to further explore these issues in more detail in future studies.

The main analyses relied on retrospective self-assessment of duration since first cannabis use rather than prospective self-report or objective drug screens.³⁴ The main predictor variable did not capture cumulative exposure to cannabis. It is feasible that some cohort members may have started cannabis use at a relatively young age and then stopped. These subjects would have been allocated the same duration since first cannabis use as those with early and persistent usage. Those with psychosis-related outcomes may have been less reliable in estimating the age at first using cannabis, but there is no a priori reason to suspect that these individuals would systematically underreport or overreport this variable. Furthermore, the strong association between alcohol and illicit drug use assessed at the 14-year follow-up and longer duration since first cannabis use assessed at the 21-year follow-up lends weight to the validity of the later variable.

Our diagnosis of nonaffective psychosis at age 21 years was not clinically validated, and our findings related to nonaffective psychosis (which were the most fragile of the 3 psychosis-related outcomes) should be interpreted cautiously. We hope to address the clinical validity of the CIDI-derived diagnoses in the cohort in future follow-ups. Diagnostic instruments were not administered at the 14-year follow-up; thus, we cannot confidently exclude the possibility that some of the cohort members may have developed psychosis as young adolescents, which may have contributed to subsequent cannabis use. In addition, the assessment of psychotic-like experiences at the 14-year follow-up were based on 2 hallucination items only; no items related to delusional beliefs were available at this follow-up.

Like other birth cohort studies, attrition was evident by the 21-year follow-up.²⁵ While this was primarily due to lack of resources to track all original cohort members rather than refusal to participate, participants lost to follow-up differed on a range of variables.¹⁹ However, results of reanalyses based on imputed data were essentially unchanged from the results based on actual data. We also undertook post hoc modeling to test the robustness/fragility of our main finding in the face of "challenging" scenarios related to differential attrition. The direction and significance of the key findings persisted in these analyses.

CONCLUSIONS

Our study has demonstrated an association between duration since first cannabis use and psychosis-related outcomes in young adults. The findings are consistent with the 2 other birth cohort studies that have addressed this issue.⁶⁻⁷ Of particular interest, these findings persisted within sibling pairs, thus reducing the chance that these associations were influenced by unmeasured residual confounding. This study has also highlighted the complexity of the relationship between risk factors and mediating variables on psychosis-related outcomes, since those with early-onset psychotic symptoms were also likely to report early cannabis use. This study provides further support for the hypothesis that early cannabis use is a risk-modifying factor for psychosis-related outcomes in young adults. Apart from the implications for policy makers and health planners,¹⁵ we hope our findings will encourage further clinical and animal model-based research to unravel the mechanisms linking cannabis use and psychosis.³⁵

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