



The Effect of Age of Initiation of Cannabis Use on Psychosis, Depression, and Anxiety among Youth under 25 Years

Effet de l'âge du début de l'utilisation du cannabis sur la psychose, la dépression et l'anxiété chez les jeunes de moins de 25 ans

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Abstract

Objectives: This study was conducted to review the current state of evidence on the association between age of initiation of cannabis use and symptoms of psychosis, depression, or anxiety among youth under 25 years of age.

Methods: We conducted a systematic review of articles published prior to March 2018 by searching OVID MEDLINE, PsycINFO, EMBASE, and the references of included studies. We included comparative studies (cohort, case-control, cross-sectional) that reported on cannabis use in persons <25 years of age (exposure) and symptoms of psychosis, depression, or anxiety (outcome). We narratively synthesized the studies according to design (cohort, etc.) and psychiatric outcome. We used the Newcastle-Ottawa Scale to assess risk of bias.

Results: Of the 534 citations identified through the literature search, 23 met the eligibility criteria and were included in this review. With psychosis as the outcome, all except one study found that earlier cannabis use was generally associated with higher risks. With depression/anxiety as the outcome, 6 of the 11 included studies reported findings indicating that earlier use of cannabis was linked to higher symptom levels.

Conclusion: In persons <25 years old, greater cannabis use is associated with more psychological symptoms, especially among those with a predisposition or existing vulnerability to such outcomes (Oxford Centre for Evidence-Based Medicine level 3 or 4). Policy makers need to consider the adverse effects of cannabis use in youth when planning a public health approach to cannabis legalization.

Abrégé

Objectifs : Cette étude a été menée pour examiner l'état actuel des données probantes sur l'association entre l'âge de début de l'utilisation du cannabis et les symptômes de psychose, de dépression ou d'anxiété chez les jeunes de moins de 25 ans.

Méthodes : Nous avons mené une revue systématique des articles publiés avant mars 2018 en cherchant dans les bases de données OVID MEDLINE, PsycINFO, EMBASE, et les bibliographies des études incluses. Nous avons inclus des études comparatives (cohorte, cas-témoin, transversale) qui portaient sur l'utilisation de cannabis chez des personnes âgées de <25 ans (exposition) et les symptômes de psychose, de dépression ou d'anxiété (résultat). Nous avons synthétisé les études sous forme narrative conformément à la méthode employée (cohorte, etc.) ainsi qu'au résultat psychiatrique. Nous avons utilisé l'échelle Newcastle-Ottawa pour évaluer le risque de biais.

Résultats : Sur les 534 citations repérées dans la recherche sur la littérature, 23 satisfaisaient aux critères d'admissibilité et ont été incluses dans cette revue. En fonction de la psychose comme résultat, toutes les études sauf une constataient que l'utilisation précoce du cannabis était généralement associée à des risques plus élevés. En fonction de la dépression/anxiété

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comme résultat, six sur 11 études incluses présentaient des résultats indiquant que l'utilisation précoce du cannabis était liée à des niveaux de symptômes plus élevés.

Conclusion : Chez les personnes de <25 ans, l'utilisation plus importante du cannabis est associée avec un plus grand nombre de symptômes psychologiques, particulièrement chez les personnes qui ont une prédisposition ou une vulnérabilité existante à ces résultats (centre Oxford de médecine fondée sur des données probantes niveau 3 ou 4). Les décideurs doivent tenir compte des effets indésirables de l'utilisation du cannabis chez les jeunes lorsqu'ils planifient une approche de santé publique pour la légalisation du cannabis.

Keywords

cannabis, psychosis, depression, anxiety, youth, age at initiation

Cannabis is the most commonly used drug in the world following tobacco and alcohol.¹ Among Canadians aged 15 years and older, an estimated 43% have used cannabis in their lifetime.² According to the United Nations Office on Drugs and Crime,³ the number of people using cannabis is rising and is estimated to be between 142.6 to 190.3 million globally. Furthermore, the prevalence of its use is very high among youth aged 25 years or younger.⁴

The prevalence of cannabis use among adolescents has caused concerns regarding its potential effects on mental health and psychiatric morbidity. Some studies have suggested that adolescent cannabis use might have long-term impacts on various neurotransmitter systems,⁵ possibly leading to psychotic,⁶ depressive, and anxiety symptoms.^{6,7}

Canada has undertaken a policy process to legalize and regulate cannabis nationally, beginning October 17, 2018. Different jurisdictions have recommended different minimum ages for cannabis use. Considerations for establishing a minimum age include health protection; the age should be set above the exposure threshold that is associated with higher than average risks of disease.

To our knowledge, no previous study has synthesized the literature on the association between cannabis use among youth and mental health outcomes to inform policy on the minimum age for cannabis use. To address these gaps and inform health policy, this study was conducted to review the published literature on cannabis use and psychosis, depression, and anxiety outcomes among youth younger than 25 years.

Methods

Study Objective

This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines⁸ and included studies meeting the following eligibility criteria (see online appendix).

Types of studies: Cohort, cross-sectional, and case-control.

Length of follow-up: No restriction.

Types of participants: Cannabis-using adolescents (aged 12-17 years) and young adults (aged 18-25 years) or studies that dichotomized age of initiation of cannabis use (i.e., <18 years

vs. ≥ 18 years [no upper age limit]) to compare early versus late initiation regardless of the source population.

Types of exposure: Cannabis use of any frequency, potency, amount, and duration during adolescence or young adulthood (<25 years).

Types of outcome: Psychosis, depression, or anxiety symptoms or disorders, using any method of diagnosis.

Timing: No restriction on length of follow-up.

Setting: No restriction on the setting of the study (e.g., community based, school based, hospital based).

Language: Restricted to English-language studies.

Search Strategy

We searched the following databases from inception to March 2018: MEDLINE (OVID interface, 1946 onwards), EMBASE (OVID interface, 1974 onwards), and PsycINFO (OVID interface, 1806 onwards).

Search

Our literature search criteria were developed with the help of a medical librarian. The following search terms were used to search the databases: *cannabis*, *marijuana abuse*, *marijuana smoking*, *depression*, *depressive disorders*, *anxiety*, *anxiety disorders*, *psychosis*, *psychotic disorders*, *schizophrenia*, *age and initiation*, and *age at onset* (see online appendix).

Study Selection

Two independent raters used the eligibility criteria to screen the retrieved citations at 1) title/abstract and 2) full text. The following information was extracted from each included study: details (i.e., author, year), sample characteristics (i.e., age, sex), design, exposures, outcomes, and covariates included in analyses. Any disagreements were resolved by a third rater, who brought the original raters together to discuss discrepancies and reach consensus. Risk of bias was assessed by one rater using the Newcastle-Ottawa Scale⁹ (see online appendix).

In this review, the beta coefficients are from linear regression models, and as such, they represent differences in means, whereas in log-transformed models, the exponentiated

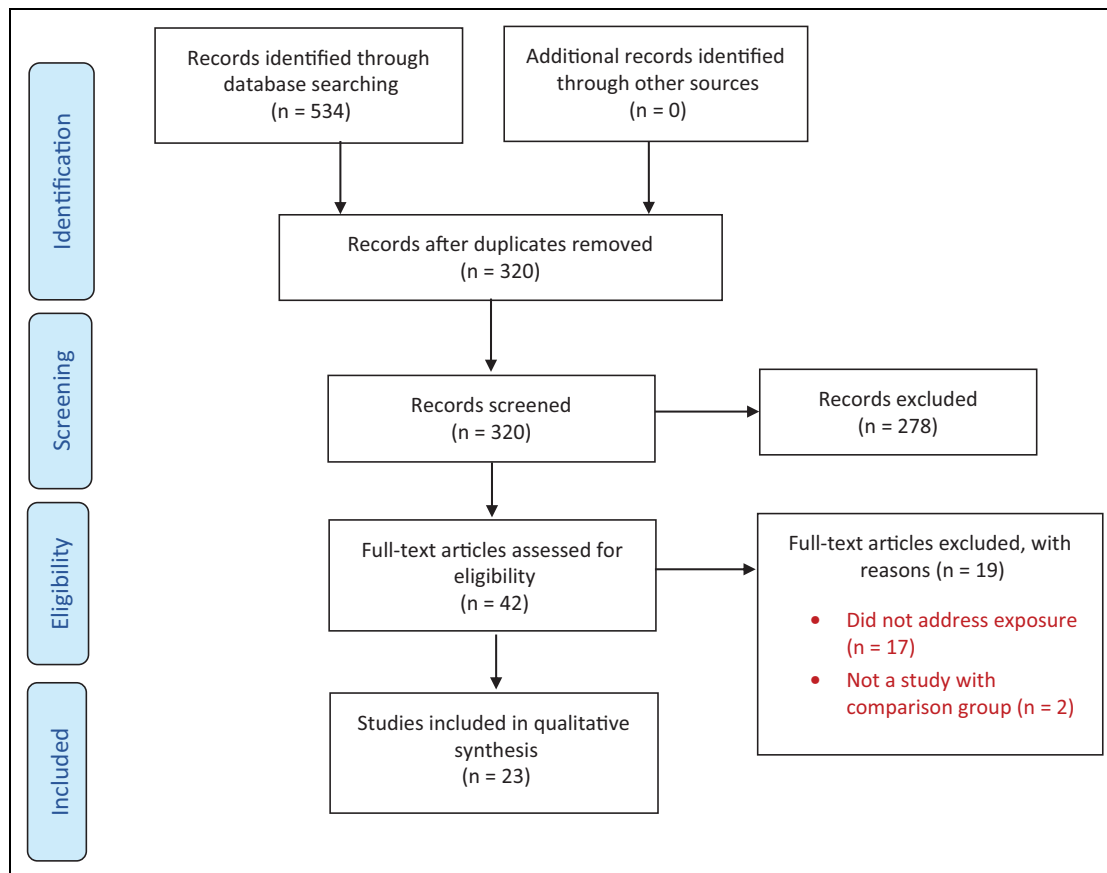


Figure 1. Article flow through the screening process.

coefficients (e.g., hazard ratio [HR], odds ratio [OR], adjusted OR [aOR]) have been reported.

Results

The literature search retrieved a total of 534 studies. Following duplicate removal ($n = 214$ studies), 320 studies entered the screening process. We excluded 278 studies (see online appendix) during title and abstract screening and 19 studies at full-text screening. The remaining 23 studies met our eligibility criteria and were included in the review. Figure 1 depicts study flow through the screening process.

Of the 23 included studies, 13 were cohort,¹⁰⁻²² 7 were cross-sectional,²³⁻²⁹ and 3 were case-control.³⁰⁻³² See the online appendix for study characteristics and risk of bias assessments.

Cannabis Use and Psychosis

Twelve of the 23 included studies examined psychosis. Overall, most found that earlier initiation of cannabis use in youth was associated with greater psychotic symptomatology, compared with later initiation or no use.

Cohort studies. Seven cohort studies^{10,13,15,19-22} enrolled samples ranging in size from 410²¹ to 45,570.¹⁹ Samples were

drawn from community settings in 5 studies^{10,13,15,21,22} and military conscripts in 2 studies.^{19,20} The age of initiation of cannabis use was between 14 and 24 years. The investigators tended to recruit participants across an age range that varied from 14 to 24 years,¹⁵ 15 to 18 years,²² or 18 to 21 years.^{13,19} Lengths of follow-up went from a minimum of 4 years¹⁵ to a maximum of 26 years.¹⁹ The investigators referred to outcomes of interest primarily in general terms (i.e., psychotic or psychiatric symptoms, or psychosis)^{10,13,15,21}; 3 studies examined schizophrenia as the outcome.^{19,20,22}

Results generally showed that earlier cannabis use among youth was associated with the aforementioned outcomes, with some evidence of ‘length of use’ effects in specific studies. However, trends in the magnitude of effect were not evident across studies with different lengths of follow-up. In studies with general psychiatric outcomes, the aOR was 1.67 (95% confidence interval [CI], 1.13 to 2.46) between ages 14 to 24 years,¹⁵ and the rate ratio was 3.7 (95% CI, 2.8 to 5.0) in 18-year-olds and 2.3 (95% CI, 1.7 to 3.2) in 21-year-olds.¹³ One study found no differences in terms of psychotic outcomes between early onset chronic users, late-onset increasing users, adolescence-limited users, and low/nonusers ($\chi^2 = 0.71$, $P > 0.05$).¹⁰ Younger age at first cannabis use was associated with an earlier age at onset of psychosis, even after adjustment for gender and duration of use (HR,

1.40; 95% CI, 1.06 to 1.83). Using high-potency cannabis daily was associated with the earlier onset of psychosis (mean [SD] years = 25.2 [6.3], median years = 24.6), compared to never using cannabis (mean [SD] years = 31.4 [9.9], median years = 30.0; HR, 1.99; 95% CI, 1.50 to 2.65).²¹

Among the schizophrenia studies, persons who used cannabis by age 15 had higher odds of developing schizophrenia symptoms at age 26 years (OR, 4.50; 95% CI, 1.11 to 18.21) compared to persons who used cannabis by age 18 years (OR, 1.65; 95% CI, 0.65 to 4.18).²² Another study found the relative risk (RR) for developing schizophrenia among high-frequency consumers to be 3 (95% CI, 1.6 to 5.5) for 11 to 50 times of cannabis use compared to no use and 6 (95% CI, 4.0 to 8.9) for >50 times of cannabis use relative to no use.²⁰ Over 26 years of follow-up, the aOR for ever users compared to no users was 1.2 (95% CI, 1.1 to 1.4).¹⁹

Case-control studies. One study of cannabis-using sibling pairs (mean age, 20 years) found an association between earlier age of initiation of cannabis use and psychotic outcomes, adjusting for age and sex ($F_{1, 213} = 18.5$; $P < .001$). For those with longer duration since first cannabis use (≤ 6 years), there was a significant elevated risk of nonaffective psychosis (aOR, 2.2; 95% CI, 1.1 to 4.5), being in the highest quartile of the Delusion Inventory Score (aOR, 4.2; 95% CI, 4.2 to 5.8), and hallucinations (aOR, 2.8; 95% CI, 1.9 to 4.1).³²

Cross-sectional studies. Four included studies were cross-sectional. Two studies investigated the association of interest among people with previous psychosis experiences.^{23,25} These studies recruited individuals with nonaffective psychosis or schizophrenia-spectrum disorder (mean age at cannabis initiation <18 years) and reported a significant association between age at initiation of cannabis use and age at onset of psychosis and schizophrenia-spectrum disorders ($\beta = 0.4$; 95% CI, 0.1 to 0.7²⁵; $\beta = 1.59$, SE = 0.27²³), as well as age at first hospitalization following psychosis onset ($\beta = 0.4$; 95% CI, 0.1 to 0.8).²⁵

Two cross-sectional studies contained samples with no predisposition to psychosis.^{27,29} Among 17,968 individuals with a mean age of 21 years, those who started using cannabis at age 12 or earlier (vs. ages 15-18 years) were more likely to score in the top 10% on psychotic experiences indicating more psychotic symptoms (OR, 3.1; 95% CI, 2.1 to 4.3). Initiation of use between the ages of 12 and 15 years (compared to 15-18 years) was associated with an OR of 1.2 (95% CI, 1.0 to 1.3).²⁹ Furthermore, among youth aged 12 to 23 years, those who first used cannabis prior to age 14 years exhibited a higher risk of experiencing psychotic symptoms ($\beta = 0.71$; 95% CI, 0.22 to 1.19) but not after age 14 years ($\beta = <@150>0.11$; 95% CI, <@150>0.57 to 0.36).²⁷

Cannabis Use and Depression and Anxiety

This review identified 11 studies on the association between adolescent cannabis use and depression or anxiety.

Cohort Studies

In total, there were 6 cohort studies. In 1 study, the results indicated greater than a 5-fold increase in the odds of developing depression or anxiety after adjustment for several confounders among female (but not male) secondary school students aged 14 to 15 years who were daily cannabis users and were followed for 7 years (females: OR, 5.6; 95% CI, 2.6 to 12; males: OR, 1.1; 95% CI, 0.55 to 2.6). Weekly or more frequent use was associated with a 2-fold higher odds of future depression and anxiety (OR, 1.9; 95% CI, 1.1 to 3.3).¹⁷ Furthermore, among 3239 Australian young adults who were followed from birth to the age of 21 years, following adjustment for confounding factors, cannabis use prior to age 15 years (vs. late onset of use) and more frequent use at 21 years were associated with greater reporting of anxiety and depression symptoms in early adulthood (OR, 3.4; 95% CI, 1.9 to 6.1), and this association existed and was similar in magnitude irrespective of mere use of cannabis versus concurrent cannabis and other illicit drug use.¹⁴

In contrast, several cohort studies failed to detect any significant effects for cannabis use prior to age 25 years and later symptoms of depression or anxiety. Using data from 45,087 Swedish conscripts aged 18 to 20 years, no associations between use prior to age 18 to 20 years and higher risk for future depression outcomes were found (adjusted HR, 1.0; 95% CI, 0.7 to 1.2).¹⁶ Examining cannabis use prior to age 15 years and rates of developing anxiety and depression during the period from age 15 to 16 years among 927 children revealed that although the odds of the outcomes were about 3 times higher for early cannabis users than for those who did not use before the age of 15 years (depression: OR, 2.9 [95% CI, 1.6 to 5.1]; anxiety: OR, 2.7 [95% CI, 1.5 to 5.0]), there were no significant differences in risk following adjustment for several confounders (depression: OR, 1.4 [95% CI, 0.7 to 2.7]; anxiety: OR, 1.2 [95% CI, 0.5 to 2.8]).¹² Furthermore, long follow-ups of 1943 adolescents (mean age, 14.9 years at baseline)¹² and 2033 individuals (baseline mean age, 14 years)¹⁸ found no significant relationship between cannabis use during adolescence and depression at age 29 years (weekly + use: adjusted for alcohol, other drug use, and adolescent anxiety and depression: OR, 1.1; 95% CI, 0.6 to 1.9)¹² or early onset (<16 years) cannabis use and later depression.¹⁸ Similarly, there was no significant association between cannabis use at age 21 years and depression outcome at age 27 years (up to 10 times use: aOR, 1.4 [95% CI, 0.8 to 2.1]; 11+ times use: aOR, 0.9 [95% CI, 0.4 to 2.5]).¹⁸

Case-control studies. Investigating the relationships between marijuana use, psychiatric symptoms, and cortisol levels in

122 persons between the ages of 13 and 23 years included the evaluation of psychiatric symptoms, midday salivary cortisol, and salivary cytokine levels. The results revealed similar cortisol and salivary cytokine levels among cannabis users and nonusers but more self-reported and clinician-rated anxiety-associated symptoms among cannabis users only (self-reported: phobic anxiety among high cannabis users vs. controls: $P = 0.0007$; obsessive-compulsive anxiety among high cannabis users vs. controls: $P = 0.006$; clinician rated: anxiety among high cannabis users vs. controls: $P = 0.0005$). Furthermore, cannabis users with greater lifetime exposure demonstrated more anxiety symptoms compared to those with lower use ($r = 0.29$, $P = 0.021$), and those with longer abstinence periods demonstrated less anxiety symptoms ($r = 0.31$, $P = 0.017$).³⁰ A case-control study of 85,088 subjects from 17 participating countries in a population-based World Health Organization world mental health survey³² examined the association of interest with local area matching of cases and controls and controlled for sex and age. Despite finding a modest association between cannabis use before age 17 years and prevalence of reporting a depression episode (RR, 1.5; 95% CI, 1.4 to 1.7), following adjustment for childhood conduct problems and early rule violations, this association was reduced to nonsignificance.³²

Cross-sectional studies. A total of 3 cross-sectional studies were included, which reported weak to modest associations. Among 16- to 18-year-old cannabis users, there were more depressive symptoms compared to controls, and cannabis use was predictive of higher levels of depressive symptomatology ($\beta = 0.42$, $P < 0.005$). Among users only, there was an interaction between cannabis use and white matter volume such that the white matter volume was negatively associated with depression symptomatology among users only.²⁸ Examining data from 1941 men from the 1944 to 1954 birth cohort found that early cannabis initiation (≤ 16 years) and depression in adulthood were weakly associated with one another, and this relationship was mediated by educational attainment, employment, and marital status ($b = 1.52$, $\beta = .05$, $P < 0.05$).²⁶ Furthermore, early onset (< 18 years) and adult-onset cannabis use among community-dwelling individuals had a modest increased odds of experiencing a depression episode compared to nonusers (early onset: OR, 1.7, $P < 0.001$; adult onset: OR, 1.8, $P < 0.001$).²⁴

Sex Differences in Relation to Cannabis Use and Symptoms of Psychosis, Depression, and Anxiety

Only 1 of the 23 included studies stratified the analysis by sex and reported separate results for females and males. Some of the studies treated sex/gender as a covariate in regression analyses but did not stratify the results of their analyses by sex/gender.

Of the studies that investigated psychosis as the main outcome, all detected significant differences between cannabis use and psychosis among all participants independent of their sex. Furthermore, of those studies that controlled for the confounding effect of sex in their analyses, some found male sex to be an additional independent risk factor for an earlier psychosis onset.²⁰ Since males generally initiate cannabis use earlier, and cannabis use is higher among males than females, males may be particularly at risk of early onset of psychosis.

Regarding depression and anxiety, only 1 of the 11 included studies compared the outcome between sexes and reported findings indicative of sex-based differences among daily cannabis-using adolescents.¹⁷ The remaining included studies did not report any findings regarding differences in these outcomes based on sex.

Assessment of Risk of Bias

This study assessed the risk of bias of the studies included using the Newcastle-Ottawa Scale (NOS). Variants of the NOS were administered for cross-sectional, cohort, and case-control studies. Figures 2 and 3 depict the percentage of cohort and cross-sectional studies that examined psychosis outcomes, as well as cohort studies that examined depression or anxiety outcomes, and satisfied each NOS criterion (received at least 1 'star' in each category). We did not produce risk of bias figures for other types of studies included in the review because their numbers were too small to depict graphically.

Regarding psychosis as the main outcome, most of the cross-sectional studies failed to justify their included sample sizes and did not elaborate on nonrespondents' characteristics. In cohort studies, exposure was primarily ascertained through self-report (also for the cross-sectional studies), and several studies did not include adequate lengths of follow-up (follow-ups that assess individuals several years after their teens and young adulthood in their 30s and later to examine the effects).¹⁰ With regard to depression/anxiety as the study outcome, the cohort studies failed to show that the outcome was not present at the start of the study and primarily used self-report to determine exposure. The bulk of the included studies received a score of medium in terms of risk of bias. Refer to the online appendix for details of the individual studies.

Discussion

Many of the included studies provided evidence of an association between cannabis use prior to age 25 years and psychotic outcomes, especially among youth with preexisting vulnerabilities. The subset of studies comparing different ages of initiation of cannabis use^{27,29} did not show that early onset cannabis use by itself is sufficient to precipitate psychotic illness. Rather, early onset use is one component of an interrelated system wherein a combination of

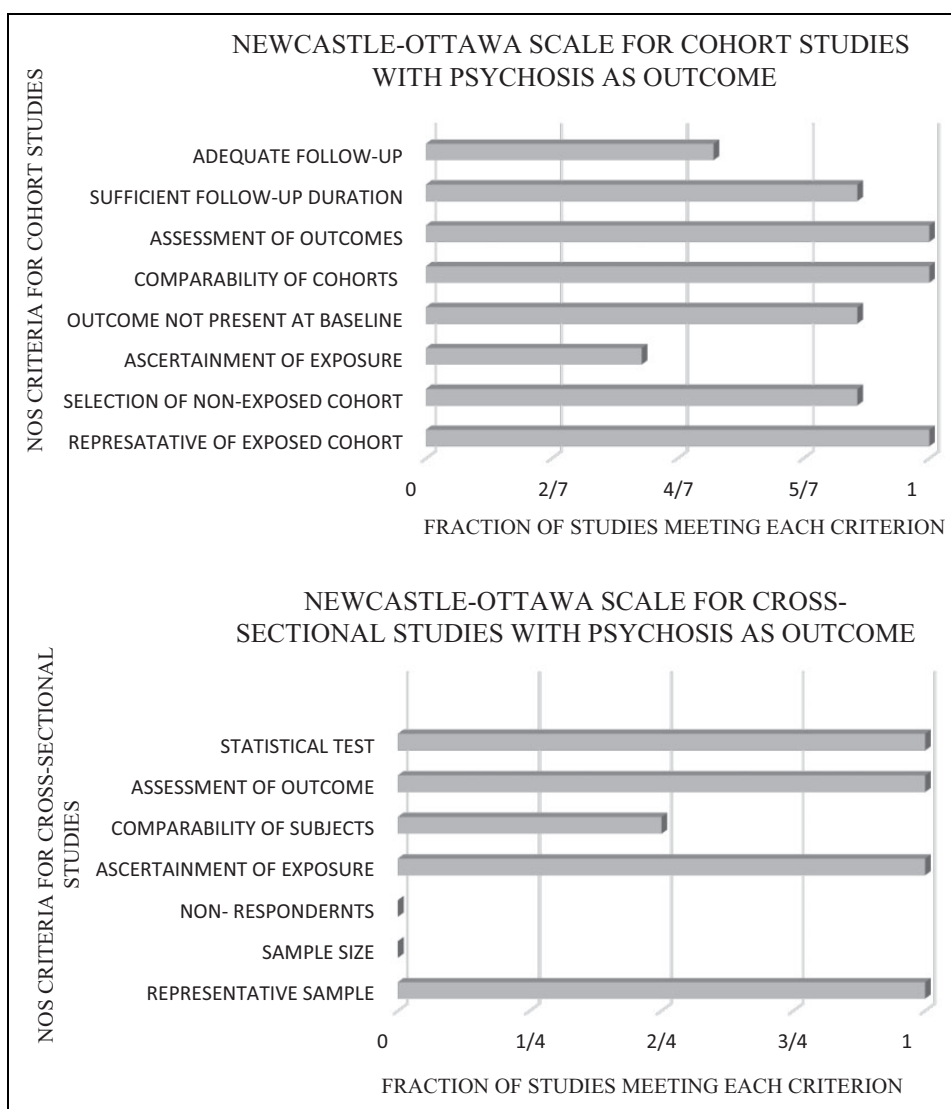


Figure 2. Newcastle-Ottawa Scale risk of bias assessment for cohort and cross-sectional studies with psychosis as outcome.

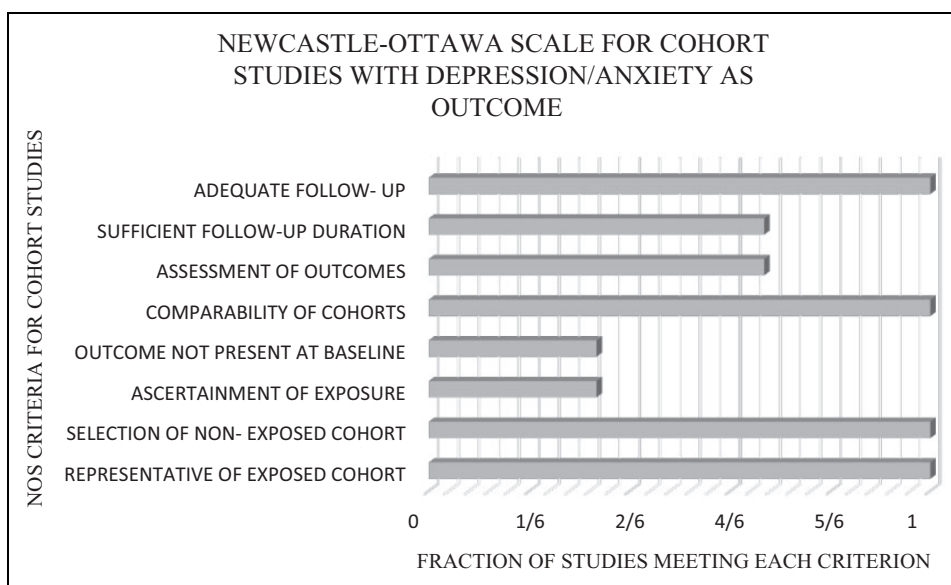


Figure 3. Newcastle-Ottawa Scale risk of bias assessment for cohort studies with depression/anxiety as outcome.

different genetic dispositions and environmental factors coalesces to produce psychotic symptoms.³³ Following the Oxford Centre for Evidence-Based Medicine Levels of Evidence,³⁴ the level of evidence from the included studies falls between levels 3 and 4, which corresponds to low evidence for using the findings to suggest a minimum age for cannabis use.

Our results indicated a less clear link between adolescent cannabis use and depression. Cannabis use may adversely influence educational attainment, employment status, and relationships, as well as indirectly affect depressive symptoms through changes in these factors. The relationship between cannabis use and anxiety symptoms appears more complex, with some findings suggesting that cannabis use may be associated primarily with acute and short-term anxiety symptoms.³⁵ However, in the long run, some individuals may use cannabis to cope with anxiety. The level of evidence from the included studies regarding the depression/anxiety as the study outcome also falls between levels 3 and 4 corresponding to a low evidence level for using the results to recommend a minimum age for cannabis use.

Limitations of Existing Studies

The included studies demonstrated heterogeneity in methods and recruitment that limited our ability to draw an overall set of clear conclusions. Few studies measured cannabis exposure among early users in great detail (i.e., onset, type, frequency, potency, amount, duration), which is crucial to understanding whether and how cannabis use influences mental health symptoms. The included studies occasionally omitted important confounding factors such as concomitant tobacco, alcohol, or other drug use; medical or mental health comorbidities; and other psychosocial factors (e.g., substance-using peers).^{21,23,24,29} The retrospective measures employed by many of the studies prevented one from teasing apart the effect of cannabis use at an early age from cumulative exposure to cannabis over time. All of the included studies used self-report measures of cannabis use, which could lead to underestimates of true effects due to social desirability and recall bias (particularly in studies with military conscripts with more severe recall bias). Last, the cross-sectional nature and lack of adequate follow-up periods of 10 (7 cross-sectional and 3 case-control) of the studies prevented us from accurately assessing the temporal relationship between early onset cannabis use and psychiatric outcomes.

Finally, we did not perform a meta-analysis because the included studies were heterogeneous in terms of source populations and samples, lengths of follow-up, and measures of exposure and outcome. A meta-analysis was further precluded because many studies did not report between-group data regarding the mean scores of outcome measures (psychosis, depression, anxiety) across different exposure groups (i.e., young cannabis users and nonusers).

Future Directions

To improve our understanding of the relation between onset of cannabis use prior to age 25 years and psychiatric outcomes, future research needs to use rigorous and prospective methodological designs. These designs need to control for confounding elements (e.g., psychiatric comorbidities; family history of psychiatric disorders; type, quantity, duration, and frequency of cannabis use; multisubstance use) to further assist our understanding of various aspects of cannabis use that may or may not be related to each of these mental health effects. Furthermore, more specific prospective clinical studies, such as the Saguenay Youth Study (SYS) in Canada³⁶ and the Adolescent Brain and Cognitive Development (ABCD) study in the United States,³⁷ can be used to study the specific elements of cannabis use that may be associated with psychiatric conditions among youth. Cohort studies that actively recruit youth at the start of their teenage years and follow them over time would be ideal. These participants would have to have no known psychiatric illness at the time of recruitment. Follow-up could persist for at least a decade and exposure assessment would involve a combination of tetra-hydro-cannabinol (THC) measures and self-report. These studies would be quite expensive and time-consuming, though, and the data would not be available to inform clinical practice and health policy for some time. In the absence of existing studies with such an optimal design, clinicians and policy makers should be aware of the limitations of current research.

From a policy perspective, more work needs to be done to recognise the predisposing risk factors related to illicit cannabis use, reasons for the induction of cannabis use, and the directness of a link between cannabis use and psychiatric symptomatology.

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Supplemental Material

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