INPLASY

Age at Onset of Psychosis Among Cannabis Users: A Meta-analysis of Temporal Factors

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ADMINISTRATIVE INFORMATION

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INTRODUCTION

*R*eview question / Objective 1. a. To estimate the pooled study-level mean age at onset (AAO) of psychosis among cannabis users with psychosis
1.b. To examine moderators of study-level mean age at onset (AAO) of psychosis among cannabis users with psychosis
2. a. To estimate the pooled mean interval between age at first cannabis use and onset of psychosis among cannabis users with psychosis.
2.b To examine moderators, the pooled mean interval between age at first cannabis use and onset of psychosis among cannabis users with psychosis.

Rationale Cannabis use is associated with an increased risk of psychotic disorders, including schizophrenia and related non-affective psychoses [Moore et al., 2007]. This risk appears greater among those who initiate use at a younger age [Kiburi et al., 2021]. Beyond increasing risk, cannabis use is also associated with an earlier onset of psychosis. Although this association is well established, the magnitude, timing, and developmental implications of this relationship remain incompletely characterised.

Previous research has largely focused on comparisons of age at onset (AAO) between cannabis users and non-users. In a 2011 meta-analysis, Large et al. reported that cannabis use was associated with a 2.7-year earlier onset of psychosis. In 2012, Myles et al. found that tobacco use was not associated with earlier onset, concluding that cannabis was more likely to play a causal role in accelerating psychosis onset.

These user–non-user comparisons have an important methodological strength: they do not depend on a uniform definition of onset, provided that whatever definition was used (e.g., first symptoms, diagnosis, treatment, or admission) was applied consistently to both users and non-users within each study.

In contrast, meta-analyses estimating the actual mean AAO among cannabis users have not been widely undertaken. This may reflect concern that AAO varies according to how onset is defined, and that study-level estimates may be confounded by demographic or clinical factors influencing AAO more generally. However, synthesising study-level mean AAO among cannabis users would permit examination of moderators and provide clinically meaningful age benchmarks.

In 2016, Myles et al. conducted a meta-analysis of the interval between first cannabis use and psychosis onset, pooling ten studies and reporting a mean delay of 6.3 years. The modest number of studies limited the exploration of moderators. By 2026, a substantially larger body of primary research will permit more detailed quantitative investigation of both methodological and clinical factors influencing AAO among cannabis users and the interval between first use and onset. One plausible moderator of both outcomes is age at first cannabis use.

To our knowledge, no meta-analysis has estimated the pooled study-level mean AAO of psychosis specifically among cannabis users. Establishing this mean would clarify the developmental stage at which cannabis-associated psychosis typically emerges. Such information is relevant to understanding disruption of educational, occupational, and social milestones, and to informing age-targeted clinical services.

Similarly, synthesising the interval between first cannabis use and psychosis onset can inform questions of epidemiological causation. If cannabis contributes to the emergence or acceleration of psychosis, exposure would be expected to precede onset by a measurable and developmentally plausible interval. A relatively consistent lag across studies would strengthen the temporal ordering criterion central to causal inference frameworks. Conversely, minimal or highly variable intervals would be more compatible with reverse causation, shared vulnerability, or cannabis use emerging during the prodrome.

Both the pooled mean AAO among cannabis users and the exposure–onset interval may also vary in light of secular changes in cannabis potency, frequency of use, and age at initiation. Rising tetrahydrocannabinol concentrations and earlier uptake in some settings raise the possibility that onset timing and lag periods have shifted over time.

The present study moves beyond simple user–non-user contrasts toward a more detailed characterisation of timing within exposed populations. Specifically, we aim to estimate (1) the pooled study-level mean AAO of psychosis among cannabis users; (2) the pooled mean interval between first cannabis use and psychosis onset; and (3) whether age at first cannabis use moderates both AAO and the exposure–onset interval.

We hypothesize that earlier age at first cannabis use will be associated with earlier onset of psychosis and a shorter interval between first use and illness onset.

Condition being studied Psychosis, including Non-affective psychosis, including schizophrenia-spectrum disorders, and other non-organic conditions characterised by hallucinations, delusions, and impaired reality testing.

METHODS

Search strategy (Psychosis or Schizophreni* or psychotic or schizoaffective) AND (Cannabis or THC) in English-language publications from inception in MEDLINE, Embase, and PsycINFO.

Participant or population Individuals of any age presenting with psychosis and a documented cannabis use history.

Intervention This is an observational study.

Comparator Not required for primary pooled mean estimates.

Study designs to be included Peer-reviewed cohort and case-control studies reporting the mean and standard deviation (or convertible statistics) for age at onset among cannabis users and the mean age at first cannabis use among people with psychosis.

Eligibility criteria Inclusion criteria:
• Cohort or case-control studies of non-affective psychosis
• Reported mean age at onset among cannabis users and the mean age at first cannabis use
• Sufficient data to calculate pooled mean estimates

Proxies for age at onset (e.g., first symptoms, first hospitalisation) will be included if consistently defined within study samples.

Exclusion criteria:
• Substance-induced psychosis
• Case reports
• Non-English publications.

Information sources Electronic data bases, reference lists of included studies and relevant reviews and meta-analysis.

Main outcome(s)
1. Pooled mean age at onset of psychosis among cannabis users.

2. Pooled mean age at first cannabis use among people with psychosis.

3. Pooled mean interval between age at first cannabis use and onset of psychosis (derived where data permit).

Additional outcome(s) Mixed-effects meta-regression will be conducted to explore sources of between-study heterogeneity in mean age at onset among cannabis users and the interval between first use of cannabis and the onset of psychosis.

Prespecified covariates will include:

Exposure-related moderators

• Mean age at first cannabis use

• Mean age at first heavy or regular use

• Proportion meeting criteria for cannabis use disorder

• Definition of cannabis exposure (any use vs regular/heavy vs CUD)

Methodological moderators

• The year of publication

• The geographic region of the publication

• The proportion of men

• The proportion of subjects diagnosed with schizophrenia

• Definition of age at onset (first symptom, first diagnosis, first hospitalisation)

• Retrospective vs prospective assessment of cannabis exposure

• First-episode vs mixed/chronic samples

• Study design (cohort vs case-control)

• Study the strength of the reporting score

• Study-level mean age at onset among non-cannabis users will be collected as a proxy for all study-level characteristics.

Meta-regression findings will be interpreted as exploratory and subject to ecological limitations. Associations observed at the study level will not be assumed to represent individual-level causal relationships.

Data management ML and CS will retain all data in duplicate.

Quality assessment / Risk of bias analysis Study quality will be assessed using a modified reporting scale adapted from Myles et al. (2012), examining:

• Representativeness of samples - whether patients were recruited from consecutive presentations or by other means for research.

• Diagnostic ascertainment - whether systematic measures, such as structured interviews, were used to diagnose use of both substances.

• Measurement and definition of cannabis exposure – whether there was an indication of the extent of cannabis use

• Definition and ascertainment of age at onset - whether the age at onset of psychosis referred to the age at onset of positive psychotic symptoms or to age at first treatment or hospital admission for psychosis.

Strategy of data synthesis Random-effects meta-analysis will be used to generate pooled mean estimates.

Statistical heterogeneity will be assessed using the I^2 statistic and between-study variance (τ^2).

Publication bias will be assessed by examination of Forrest Plots and Eggers regression.

Mixed-effects meta-regression will examine whether variability in pooled estimates is associated with prespecified exposure-related and methodological characteristics. Given the reliance on aggregate data, analyses will be interpreted cautiously within an epidemiological framework, recognising the limitations of ecological inference.

Subgroup analysis
Where data permit:
• First-episode samples
• Cannabis use disorder vs any use
• Early-onset psychosis samples.

Sensitivity analysis Sensitivity analyses will exclude studies with a high risk of bias and studies using proxy measures of age at onset.

Language restriction English.

Country(ies) involved Australia.

Keywords Cannabis; marijuana; THC; psychosis; schizophrenia; age at onset; temporality; epidemiology; causation.

Dissemination plans Publication in a peer-reviewed journal. The data will be made available in a supplement.

Contributions of each author
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