

**Cannabis Use and the Age of Onset of Psychosis:
a Replication and Extension Meta-analysis**

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ADMINISTRATIVE INFORMATION**Support** - Nil.**Review Stage at time of this submission** - Preliminary searches.**Conflicts of interest** - None declared.**INPLASY registration number:** INPLASY202550051**Amendments** - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 19 May 2025 and was last updated on 19 May 2025.**INTRODUCTION**

Review question / Objective 1. To determine if the findings of the 2011 Large et al. meta-analysis are conserved upon inclusion of recent publications

2. To determine if there is a dose-response relationship for cannabis and AOO of psychosis
3. To determine if there is an association between age of initial cannabis use and AOO of psychosis
4. To determine if the effect size of the association between cannabis and AOO of psychosis differs between males and females.

Rationale In 2011, a meta-analysis by Large et al. (see below for reference) reported that cannabis use accelerates the onset of psychosis by 2.7 years on average. Since 2011, there has been an explosion of literature on cannabis and age of onset of psychosis. Given this literature expansion and the trend of increasing potency of cannabis, there is an opportunity to re-examine this association as well as investigate the effects of gender and patterns of cannabis exposure.

Large, M., Sharma, S., Compton, M. T., Slade, T., & Nielssen, O. (2011). Cannabis use and earlier onset of psychosis: a systematic meta-analysis. *Archives of general psychiatry*, 68(6), 555–561. <https://doi.org/10.1001/archgenpsychiatry.2011.5>.

Condition being studied The condition being studied is psychosis, which is a collection of symptoms (e.g. hallucinations, delusions) that impede one's ability to perceive and interpret reality. Psychosis is a common manifestation of schizophrenia-spectrum disorders, which are a debilitating set of psychiatric conditions.

METHODS

Participant or population People of any age presenting with psychosis who may or may not have indicators of cannabis use.

Intervention Independent variable is cannabis use, including lifetime exposure, current use and cannabis use disorder.

Comparator n/a.

Study designs to be included Cohort and case-control studies.

Eligibility criteria Inclusion criteria: peer-reviewed cohort or case-control studies with samples of patients with non-affective psychosis that report age of onset according to cannabis use status. Proxies for age of onset, including first hospitalisation, are included if definition is consistent between cannabis and non-cannabis groups within a study.

Exclusion criteria: Studies on affective psychosis or substance-induced psychosis, and studies published in a language other than English.

Information sources Databases (medline, EMBASE, psychoINFO), contact with authors in cases of insufficient data.

Main outcome(s) Outcome of interest is the standardised mean difference and difference in means of the age of onset of psychosis between cannabis and non-cannabis using groups.

Quality assessment / Risk of bias analysis Strength of reporting will be examined using a modified scale from Myles et al. 2012 (see below for reference). We will examine representativeness of the population (including measures of diagnosis and whether patients were drawn from an identified population group) and strength of reporting of independent variables (measures of cannabis use/exposure) and dependent variable (age of onset of psychosis).

Myles, N., Newall, H., Nielssen, O., Large, M. & Siskind, D. The association between cannabis use and earlier age at onset of schizophrenia and other psychoses: meta-analysis of possible confounding factors. *Curr. Pharm. Des.* 18, 5055–5069 (2012).

Strategy of data synthesis A random-effects meta-analysis using CMA V4 software.

Subgroup analysis Mixed-effects meta-analysis for gender and degree of cannabis exposure.

Sensitivity analysis Mixed-effects meta-analysis and meta regression for mean age of onset of psychosis per study, overall study quality using dichotomised strength of reporting score, study design and year of publication.

Country(ies) involved Australia.

Keywords cannabis; THC; marijuana; psychosis; schizophrenia.

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