

Review article

Cannabis use and subsequent onset of manic symptoms and bipolar disorder: A systematic review and meta-analysis

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ABSTRACT

Background: Bipolar disorder is a disabling psychiatric condition affecting approximately 2% of the population, for which identifying modifiable risk factors prior to illness onset is a research priority. Cannabis use is highly prevalent, yet its role in the development of bipolar-spectrum outcomes remains unclear. Previous reviews have included few studies or combined distinct bipolar-spectrum outcomes, limiting outcome-specific inference.

Aims: To evaluate the association between cannabis exposure and subsequent incident BD and manic/hypomanic symptoms separately and examine potential moderating factors.

Methods: Registered (<https://osf.io/s38x4/>), PRISMA/MOOSE-compliant systematic review and meta-analysis of PubMed and Web of Science from inception to October 2025. We included longitudinal observational studies comparing cannabis-exposed and unexposed individuals without prior BD and assessing subsequent bipolar-spectrum outcomes. We meta-analysed studies with extractable data, calculating the unadjusted risk ratios (RRs) for incident BD and manic/hypomanic symptoms. Random-effects meta-analyses, heterogeneity analyses, subgroup analyses and meta-regressions were performed. Study quality was appraised using the Newcastle–Ottawa Scale (NOS).

Results: Nineteen studies were included (total $N = 6,960,517$; mean age 23.8 ± 11.8 years; 49% female). Cannabis use was associated with increased risk of BD ($RR = 2.46$, 95% $CI = 1.57–3.84$; $k = 8$; $N = 206,572$) and

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manic/hypomanic symptoms (RR = 2.11, 95% CI = 1.07–4.18; $k = 6$; $N = 57,243$). Moderator analyses identified significant clinical and methodological sources of heterogeneity. NOS scores ranged from 6 to 9, indicating good to high methodological quality.

Conclusion: Cannabis use was associated with an increased risk of subsequent bipolar-spectrum outcomes. Routine evaluation of cannabis use alongside prevention strategies, to delay initiation and reduce use, may warranted.

1. Introduction

Bipolar disorder (BD) is a psychiatric condition marked by recurrent shifts in mood, energy and activity levels (Malhi et al., 2014; Vieta et al., 2018). It affects roughly 2% of the population and contributes substantially to global disability and functional impairment (Alonso et al., 2011; Nierenberg et al., 2023). Because BD can have profound consequences for health, relationships, education, and work, research has increasingly emphasized the identification of risk states and potentially modifiable upstream factors before the first full-threshold episode, with the aim of improving prevention and early intervention (Faedda et al., 2019; Salazar de Pablo et al., 2026). However, early recognition remains challenging because incipient presentations are heterogeneous, overlap with other psychiatric conditions and are variably defined across studies, highlighting the need to clarify potentially modifiable risk factors (Aymerich et al., 2025; Salazar de Pablo et al., 2020).

Cannabis use is prevalent among the general population, with initiation frequently occurring during adolescence (Hasin et al., 2016; Wittchen et al., 2007). While the evidence linking cannabis exposure to later psychotic outcomes is robust (Baeza et al., 2009; Aymerich et al., 2026), the impact on the development of BD has historically received less attention and remains less clearly established (National Academies of Sciences, 2017). Previous reviews on cannabis use and bipolar-spectrum outcomes have been relatively narrow in scope and included few studies (Bally et al., 2014; Bartoli et al., 2025; Gibbs et al., 2015; Maggu et al., 2023). Gibbs et al. conducted a meta-analysis reporting that cannabis use was associated with a higher risk of incident manic symptoms but included only two studies (Gibbs et al., 2015). Another meta-analysis including four studies until 2022 reported a positive association between cannabis exposure and bipolar-spectrum outcomes, but pooled together incident BD diagnoses from manic/hypomanic symptoms, limiting outcome-specific inference (Maggu et al., 2023). Other narrative reviews have addressed related questions. Bally and colleagues summarised observational evidence on cannabis use and first manic episodes without meta-analytic pooling (Bally et al., 2014), and a separate narrative perspective examined adolescent cannabis exposure in relation to later BD onset (Bartoli et al., 2025). Since these publications, the literature has expanded with new studies being published (Denisoff et al., 2022; Jefsen et al., 2023; Robinson et al., 2024).

To date, no updated quantitative synthesis has systematically examined the association between cannabis exposure and incident bipolar-spectrum outcomes, explicitly separating BD from manic/hypomanic symptoms; while formally assessing potential clinical and methodological moderators.

This systematic review and meta-analysis aims to: (a) compare the risk of incident BD and incident manic/hypomanic symptoms between individuals exposed to cannabis and those unexposed; (b) meta-analyze studies with extractable data, calculating the unadjusted risk ratios (RRs) for incident bipolar disorder and incident manic/hypomanic symptoms associated with cannabis exposure; and (c) examine whether effect estimates vary according to clinical and/or methodological moderating factors.

2. Methods

The study protocol was registered on the Open Science Framework (OSF) (<https://osf.io/s38x4/>). The systematic review and meta-analysis

were conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (eTable 1) (Moher et al., 2009) and the Meta-Analyses of Observational Studies in Epidemiology (MOOSE) checklist (eTable 2) (Stroup et al., 2000), following the EQUATOR Network reporting recommendations (Altman et al., 2008).

2.1. Search strategy and selection criteria

PubMed/MEDLINE and Web of Science Core Collection were systematically searched from inception to 27 October 2025. The following search terms were used: (“cannabis” OR “marijuana” OR “THC” OR “tetrahydrocannabinol” OR “cannabis use disorder” OR “cannabis dependence” OR “cannabis misuse” OR “CUD”) AND (“bipolar” OR “bipolar disorder” OR “mania” OR “hypomania” OR “bipolar I” OR “bipolar II” OR “bipolar affective disorder” OR “BD-I” OR “BD-II” OR “BD-NOS” OR “cyclothymic”) AND (“onset” OR “risk of progression” OR “progression to mania” OR “transition” OR “threshold” OR “development” OR “switch” OR “first episode”). In addition to database searches, we conducted manual searching by (i) screening the reference lists of all included articles, and (ii) screening the reference lists of key prior reviews and meta-analyses in this area (Bally et al., 2014; Bartoli et al., 2025; Gibbs et al., 2015).

After removing duplicates, articles identified were first screened at the title and abstract level. Full texts were then assessed for eligibility after excluding those that did not meet inclusion criteria. Study selection was performed independently by two reviewers (C.S.O., P.Q.), with discrepancies resolved by consensus, consulting a senior researcher (G.S.P.) as needed.

Inclusion criteria for the systematic review were: (a) longitudinal observational studies; (b) reporting on individuals without BD or relevant manic/hypomanic symptoms at baseline; (c) including a group exposed to cannabis, defined as cannabis use (e.g. any/ever use, frequent/heavy use) or CUD; (d) including a comparator group unexposed to cannabis (i.e., allowing a exposed vs non-exposed comparison); and (e) evaluating the incidence of BD or manic/hypomanic symptoms, assessed during follow-up, with outcomes defined using Diagnostic and Statistical Manual of Mental Disorders (DSM) or International Classification of Diseases (ICD) diagnostic criteria for BD or validated instruments to assess manic/hypomanic symptoms (e.g., AUDADIS-IV, MINI structured diagnostic interview, Hypomania Checklist-32, CIDI).

Exclusion criteria were: (a) studies assessing relapse or symptom exacerbation in individuals with previous manic symptoms or established bipolar disorder rather than first-onset events; and (b) reviews, case reports, conference abstracts, small case series ($n < 5$) and grey literature.

Additional exclusion criteria for the meta-analysis were: (a) overlapping reports from the same cohort (only the largest report per cohort per outcome was included to avoid double-counting); and (b) studies enriched for major psychiatric disorders at baseline (e.g., major depressive disorder or psychotic disorders) and diagnostic transition designs (e.g., transition from major depressive disorder or substance-induced psychosis to bipolar disorder).

2.2. Data extraction

Two researchers (C.S.O., P.Q.) independently extracted data from all

included studies using a predefined data extraction form. Extracted variables included: first author and year of publication, country and cohort or data source, sample size, age (mean $\pm$ standard deviation), sex (% female), study design, follow-up duration, definition and assessment of cannabis exposure (including measurement tool and cut-offs), outcome definition (BD or mania/hypomania symptoms), diagnostic criteria or assessment scales, effect size estimates, covariates included in adjusted models, and key findings. When necessary, corresponding authors were contacted to obtain additional information or clarify missing data.

2.3. Risk of bias (quality assessment)

Risk of bias was assessed using the Newcastle–Ottawa Scale (NOS) for observational studies, which has been repeatedly used in the field (Aymerich et al., 2025; Salazar de Pablo et al., 2025). Each study was assigned 0–9 points according to their representativeness, exposure, comparability, outcomes, follow-up period, and losses to follow-up, where lower scores indicate higher risk of bias and higher scores indicate better methodological quality (eTable 3).

2.4. Data synthesis and statistical analysis

The data synthesis was conducted in two steps: (i) narrative synthesis of included studies; and (ii) separate meta-analyses for incident bipolar disorder and incident manic/hypomanic symptoms. In each meta-analysis, we compared cannabis-exposed and non-exposed samples and estimated the crude risk of developing the outcome of interest. The two outcome categories were considered related but clinically distinct manifestations of bipolar-spectrum pathology. Therefore, they were included within the same systematic review because both addressed the longitudinal association between cannabis exposure and subsequent bipolar-spectrum outcomes, but were analysed separately to avoid combining diagnostic and symptom-based outcomes. Effect sizes were expressed as risk ratios (RRs), with a RR greater than 1 indicating a higher risk of the outcome in the cannabis-exposed group than in the non-exposed group. Crude RRs were calculated from 2×2 contingency tables using the number of incident outcome events and the total number of participants in the cannabis-exposed and non-exposed groups. Since the outcomes were rare and dichotomous, pooled estimates were calculated using the Mantel-Haenszel method (Fidler and Nagelkerke, 2013). Given the expected clinical and methodological diversity across studies, we assumed that the true effect could vary between studies and therefore used random-effects models throughout. The between-study variance (τ^2) was estimated using restricted maximum likelihood (REML) (Higgins et al., 2024).

For both outcomes, the primary analysis compared cannabis exposure versus no/never use; exposure definitions were determined by the available literature: for BD, studies included both cannabis use and CUD, whereas for manic/hypomanic outcomes, exposure was limited to cannabis use definitions (any/lifetime or frequent use).

When a study reported both bipolar disorder and manic/hypomanic outcomes, it was included in the corresponding outcome-specific meta-analysis for each outcome. When multiple follow-up assessments were reported, the longest available follow-up was selected for the primary meta-analysis. No multiple exposure definitions requiring selection between different estimates were reported among the included studies.

Subgroup analyses were conducted according to cannabis exposure definition (cannabis use versus cannabis use disorder), age group (mean sample age ≤ 18 vs > 18 years), and follow-up duration (≤ 3 vs > 3 years), where data allowed for it. Formal tests for subgroup differences were performed when applicable. The age subgroup analysis was intended to explore whether associations differed between predominantly adolescent and adult samples. The 18-year threshold was selected as a clinically interpretable boundary between adolescent and adult populations.

Between-study heterogeneity was assessed using Cochran's Q

statistic, with the proportion of the total variability in RR estimates evaluated using the I^2 index. According to the previous literature, I^2 values of 25%, 50%, and 75% were considered to represent low, moderate, and high heterogeneity, respectively (Lipsey NW, 2009).

To assess the robustness of the findings, we performed a leave-one-out sensitivity analysis by sequentially excluding each study and recalculating the pooled estimate using the same random-effects model. This analysis examined whether any individual study had a disproportionate influence on the pooled effect size or on between-study heterogeneity.

When at least five articles were available for a given outcome (Denisoff et al., 2022; Manrique-Garcia et al., 2012; Marwaha et al., 2018; Nielsen et al., 2021; Tijssen et al., 2010), we conducted random-effects meta-regressions to examine whether effect sizes varied according to a) follow-up duration (years), b) mean age as a continuous predictor, c) percentage of females, d) study quality (total NOS score), and e) publication year.

Publication bias was explored by visual inspection of funnel plots. Formal testing using Egger's regression was not performed due to the limited number of studies per outcome (< 10) as recommended given the low power of such tests (Higgins et al., 2024); therefore these assessments were considered exploratory.

All analyses were conducted in R (version 4.5.1) within the Microsoft Azure Machine Learning environment (Team, 2025) using the meta and metafor package. Statistical significance was set at a $p < 0.05$ (two-sided).

3. Results

3.1. Search results

The search identified 1053 records (1051 from databases and two from manual reference searching). After removal of 58 duplicates, 995 records were screened, and 86 full-text reports were assessed for eligibility. Sixty-seven reports were excluded (see eTable 4), leaving 19 studies, as shown in the study flow diagram (Fig. 1).

3.2. Study characteristics

Our 19 studies reported on a total of 6,960,517 participants, of whom 67,992 were cannabis users. Cannabis exposure prevalence, defined variably across studies as lifetime use, recent use, or current use, varied widely across studies (0.4%–55.6%; median 7.9%), and the overall proportion was heavily driven by the largest registry study that reported a CUD prevalence of 0.84%. Thirteen studies were included in the meta-analysis. Studies were conducted in 11 countries, most commonly the USA and the Netherlands ($n = 3$ each, 15.8%), followed by Brazil, Denmark, Sweden, and Australia ($n = 2$ each, 10.5%); Finland, the UK, Norway, Colombia, and Germany contributed one study each ($n = 1$, 5.3%). Mean age at baseline across studies was 23.8 ± 11.8 years, based on studies that reported this data, ranging from 14 to 65 years old. However, 26.3% of the studies included did not provide age and 15.8% only provided range. Notably, none of the included studies reported age of onset of cannabis use. Overall, 51.3% of participants were female in the 14 studies reporting sex distribution, although 5 studies did not report female counts. Sample sizes ranged from $n = 36$ to $n = 6,651,765$.

Of the 19 included studies, 11 (57.9%) assessed BD (Bach et al., 2021; Cougle et al., 2015; Denisoff et al., 2022; Gilman et al., 2012; Jepsen et al., 2023; Jorge et al., 2024; Ratheesh et al., 2015; Robinson et al., 2024; Service et al., 2023; van Laar et al., 2007), 7 (36.8%) assessed manic/hypomanic symptoms (Feingold et al., 2015; Henquet et al., 2006; Marwaha et al., 2018; Nielsen et al., 2021; Radhakrishnan et al., 2019; Ratheesh et al., 2018; Tijssen et al., 2010), and 1 (5%) assessed both outcomes (Manrique-Garcia et al., 2012). Study characteristics are summarised in Table 1. From the 19 studies, 6 studies were excluded from the meta-analysis following the exclusion criteria.

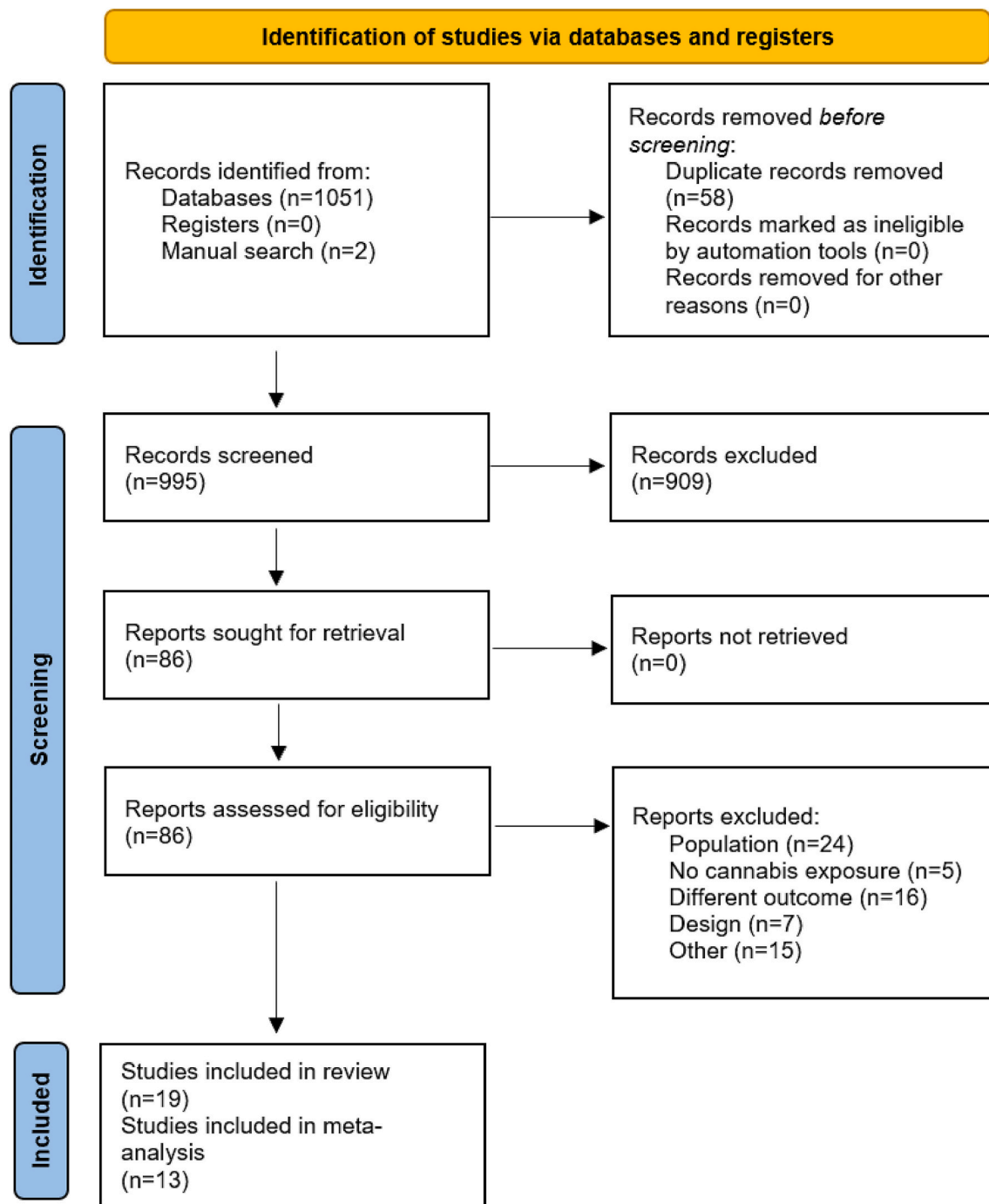


Fig. 1. Preferred reporting items for systematic reviews and meta-analyses (PRISMA) flowchart outlining the study selection process.

3.3. Meta-analysis of incident bipolar disorder

Eight studies were included in the primary meta-analysis ($k = 8$; total $N = 206,572$; 20,295 BD cases) (Cougale et al., 2015; Denissoff et al., 2022; Jorge et al., 2024; Manrique-Garcia et al., 2012; Ratheesh et al., 2015; Robinson et al., 2024; Rognli et al., 2020; van Laar et al., 2007). Overall, cannabis use (defined as any use, including CUD and non-CUD definitions across studies) was associated with a significantly increased risk of BD compared with non-use ($RR = 2.46$, 95% CI 1.57–3.8; $p < 0.0001$) (Fig. 2). Heterogeneity was substantial ($I^2 = 83.5\%$; $\tau^2 = 0.31$). Exploratory funnel plots can be found in eFigure 1.

3.4. Meta-analysis of incident mania/hypomania

Six studies were included in the meta-analysis for manic or hypomanic symptoms ($N = 57,243$; 721 cases of mania/hypomania symptoms) (Bach et al., 2021; Henquet et al., 2006; Manrique-Garcia et al., 2012; Marwaha et al., 2018; Nielsen et al., 2021; Tijssen et al., 2010). Overall, cannabis use (defined as cannabis lifetime use) was associated with a significantly increased risk of manic/hypomanic symptoms compared with non-use ($RR = 2.11$, 95% CI 1.07–4.18; $p = 0.032$) (Fig. 3). Heterogeneity was high ($I^2 = 90.5\%$; $\tau^2 = 0.64$), indicating substantial between-study variability. Given the small number of studies ($k < 10$), formal tests for small-study effects were not performed. Exploratory funnel plots can be found in eFigure 2.

Table 1
Study characteristics.

Study	Country	Follow-up duration (years)	% female	Sample size (N total/N cannabis)	Age: mean, SD (range)	Outcome/ measurement tool (type of scale)	Cannabis use and measure	Key findings	NOS
Bach et al., 2021 (Bach et al., 2021)	Brazil	5	55.2	1560/N.a.	20.6 ± 2.1 (18–24)	Bipolar disorder (MINI structured diagnostic interview)	Cannabis abuse (ASSIST 3.1, <i>cannabis involvement score</i> ≥ 4)	Cannabis abuse predicted new-onset bipolar disorder at 5 years in crude models (RR 2.38, 95% CI 1.15–4.89; <i>p</i> = 0.019), whereas the adjusted estimate was attenuated and no longer statistically significant. RR: 1.27 (0.57–2.8)	8
Cogle et al., 2015 (Cogle et al., 2015)	USA	3	N.a.	34,653/671	N.a.	Bipolar disorder (Structured interview based upon DSM-IV)	Cannabis use (Self-report, <i>weekly use</i>)	Weekly cannabis use predicted new-onset bipolar disorder over 3 years. OR: 1.38 (1.11–1.72)	8
Denissoff et al., 2022 (Denissoff et al., 2022)	Finland	17–18	51.2	6325/352	N.a. (15–16)	Bipolar disorder (ICD)	Cannabis use (Self-report, <i>lifetime use</i>)	Baseline cannabis use predicted an increased risk of later bipolar disorder. HR: 2.34 (1.11–4.94). The association was no longer significant after adjusting for heavy alcohol use, daily smoking and other drug use	9
Feingold et al., 2015 (Feingold et al., 2015)	USA	3	32.6	32,606/1029	N.a.	Mania/ Hypomania symptoms (AUDADIS-IV)	Cannabis use (AUDADIS-IV, <i>Past year use</i>)	Cannabis use at baseline predicted a significantly increased risk of incident manic/hypomanic episodes over 3 years. OR: 2.47 (1.03–5.92)	9
Gilman et al., 2012 (Gilman et al., 2012)	USA	3	N.a.	34,653/N.a.	N.a.	Bipolar disorder (Structured interview based upon DSM-IV)	Cannabis use disorder (AUDADIS-IV)	Among participants with past-year MDD, CUD was associated with increased risk of switching to bipolar disorder. OR: 2.12 (1.1–4.08)	8
Henquet et al., 2006 (Henquet et al., 2006)	Netherlands	3	53.4	4815/453	41.2 ± 11.9 (18–64)	Mania/ Hypomania symptoms (Self-report CIDI-based symptom count)	Cannabis use (CIDI-L, <i>Lifetime use</i>)	Cannabis use predicted the development of manic symptoms over 3 years in the general population. OR: 2.7 (1.54–4.75)	9
Jefsen et al., 2023 (Jefsen et al., 2023)	Denmark	27	50.3	6,651,765/55,968	N.a. (16–N.a.)	Bipolar disorder (Clinical ICD diagnosis)	Cannabis use disorder (Clinical ICD diagnosis)	Cannabis use disorder was associated with an increased risk of developing bipolar disorder: HR 2.96 (95% CI 2.73–3.21) in males; HR 2.54 (95% CI 2.31–2.80) in females. Risk was highest in the first 6 months after diagnosis and persisted for up to 10 years	9
Jorge et al., 2024 (Jorge et al., 2024)	Brazil	5	53	3712/715	18	Bipolar disorder (MINI structured diagnostic interview)	Cannabis use (Self-report, <i>lifetime use</i>)	Lifetime cannabis use measured at 18 years old predicted bipolar disorder onset over 5 years in crude and partially adjusted models OR: 2 (1.2–3.25)	9
Manrique-Garcia et al., 2012 (Manrique-Garcia et al., 2012)	Sweden	35	0	45,087/631	N.a. (18–20)	Mania and Bipolar disorder (ICD diagnosis)	Cannabis use (Self-report, <i>lifetime use^b/used >50 times</i>)	Cannabis use was not associated with subsequent bipolar disorder over 35 years of follow-up. HR: 0.96 (0.4–1.9) (mania); 1.1 (0.7–1.7) (BD). Heavy use (>50 times) was not associated with increased risk.	9
Marwaha et al., 2018 (Marwaha et al., 2018)	UK	5	64.7	3,370/61	17 ± N.a. (N.a.)	Mania/ Hypomania symptoms (Self-report hypomania checklist-32)	Cannabis use (Self-report, <i>any use^b/weekly use</i>)	Frequent cannabis use at 17 years (≥2–3 times weekly) predicted hypomania at 22–23 years. There was a dose-response relationship (any use vs weekly). OR: 2.21 (1.49–3.28)	7
Nielsen et al., 2021 (Nielsen et al., 2021)	Denmark	5	54.1	866/52	16 ± N.a. (N.a.)	Mania/ Hypomania symptoms (Self-	Cannabis use (ASSIST; <i>lifetime</i>	Cannabis use before age 16 was associated with an approximately threefold	6

(continued on next page)

Table 1 (continued)

Study	Country	Follow-up duration (years)	% female	Sample size (N total/N cannabis)	Age: mean, SD (range)	Outcome/ measurement tool (type of scale)	Cannabis use and measure	Key findings	NOS
Radhakrishnan et al., 2019 (Radhakrishnan et al., 2019)	Netherlands	6	55.4	6646/N.a.	47.3 ± 12.7 (18–65)	Mania/Hypomania symptoms ^a (CIDI 3.0)	report hypomania checklist-32) Cannabis use (CIDI 3.0; weekly use)	increased risk of subclinical hypomania at age 16. RR: 3 (1.82–4.94) ** Cannabis use was associated with higher odds of affective dysregulation with psychosis admixture. OR: 2.56 (1.56–4.2)	7
Ratheesh et al., 2015 (Ratheesh et al., 2015)	Australia	1	85	52/9	19.7 ± 2.8 (15–25)	Bipolar disorder (DSM-IV)	Cannabis use disorder (DSM-IV)	Cannabis use disorder did not predict 12-month conversion to bipolar disorder. Only unadjusted measures were reported. OR 1.7 (0.2–18.1)	6
Ratheesh et al., 2018 (Ratheesh et al., 2018)	Australia	9.6 (± 2.2)	N.a.	36/20	19.6 ± 3.7 (15–30)	Mania/Hypomania symptoms (DSM-IV)	Cannabis use (Self-report, lifetime use)	Alcohol use disorder and family history of substance use disorder were the strongest predictors. Lifetime cannabis use (65%) did not differ between those who developed mania and controls. No effect was reported.	6
Robinson et al., 2024 (Robinson et al., 2024)	Sweden	15–40	N.a.	112,086/446	N.a.	Bipolar disorder (ICD)	Cannabis use disorder (ICD)	Cannabis use disorder diagnosed ≥2 years before bipolar disorder, was associated with an increased risk of bipolar disorder. Although this estimate is unadjusted, the temporal direction is clear. IRR 8.08 (6.66–9.80)	9
Rognli et al., 2020 (Rognli et al., 2020)	Norway	9	56	2602/317	15.1 ± 2 (12–20)	Bipolar disorder (Proxied by prescription of MS)	Cannabis use (Self-report, past year use)	Past-year cannabis use predicted later prescription of mood stabilizers (proxy for bipolar disorder). OR: 5.36 (1.99–14.44)	9
Service et al., 2023 (Service et al., 2023)	Colombia	1 day to 15 years (1.6 ± 2.4 years)	66	13,607/1072	N.a.	Bipolar disorder (ICD)	Cannabis use (HER, Lifetime use)	Cannabis use was associated with a lower conversion from MDD to BD, identified through NLP clinical features. HR: 0.74 (0.56–0.99)	8
Tijssen et al., 2010 (Tijssen et al., 2010)	Germany	8.3 (7.4–10.6 ± 0.7)	47.2	1395/31	15.1 ± 1.1 (14–17)	Mania/Hypomania symptoms (DIA-X/M-CIDI mania section)	Cannabis use (DIA-X/M-CIDI substance use module, lifetime use defined as ≥5 times)	Lifetime cannabis use (≥5 times) was associated with a fourfold increased risk of incident manic symptoms over 8 years. OR: 4.26 (1.42–12.76) Cannabis did not predict persistence, only onset.	8
Van Laar et al., 2007 (van Laar et al., 2007)	Netherlands	3	46	4681/484	39 ± 12.9 (18–64)	Bipolar disorder (DSM-III-R, CIDI 1.1)	Cannabis use (CIDI 1.1, Lifetime use >5 times)	Baseline cannabis use predicted first incidence of bipolar disorder: adjusted OR 4.98 (95% CI 1.80–13.81)	8

ALSPAC: Avon Longitudinal Study of Parents and Children; CCC2000: Copenhagen Child Cohort 2000; CHDS: Christchurch Health and Development Study; CIDI: Composite International Diagnostic Interview; CSJDM: Clínica San Juan de Dios Manizales; CUD: Cannabis Use Disorder; DNR: Danish Nationwide Register Cohort; DSM: Diagnostic and Statistical Manual of Mental Disorders; EDSP: Early Developmental Stages of Psychopathology; E-Risk: Environmental Risk Longitudinal Twin Study; HS: Help-Seeking (Youth Cohort); ICD: International Classification of Diseases; MDD: Major Depressive Disorder; MINI: Mini International Neuropsychiatric Interview; N.a.: Not available (not reported); NCS: National Comorbidity Survey; NCS-R: National Comorbidity Survey Replication; NEMESIS: Netherlands Mental Health Survey and Incidence Study; NESARC: National Epidemiologic Survey on Alcohol and Related Conditions; NFBC: Northern Finland Birth Cohort; NorPD: Norwegian Prescription Database; NSDUH: National Survey on Drug Use and Health; OR: Odds Ratio; PACE: Personal Assessment and Crisis Evaluation Clinic; PBC: Pelotas Birth Cohort; RR: Risk Ratio; Swedish SNRCC: National Register Conscription Cohort; SMCC: Stockholm Metropolitan Cohort; TRAILS: Tracking Adolescents' Individual Lives Survey; UHR-P: Ultra High Risk-Psychosis; UKB: UK Biobank, YRBSS: Youth Risk Behavior Surveillance System.

Note: Effect estimates are adjusted unless otherwise specified.

^a Manic symptoms were assessed alongside other affective dysregulation symptoms, and results were reported as a combined outcome.

^b Exposure measure used for the RR estimate.

** Denotes an unadjusted effect estimate.

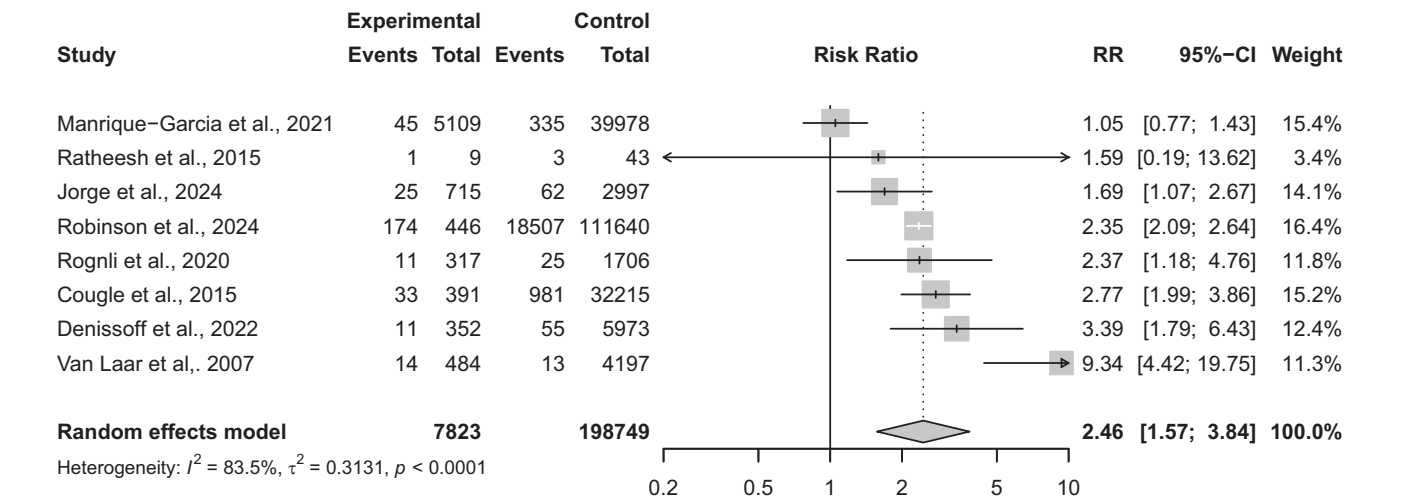


Fig. 2. Risk of incident bipolar disorder among individuals exposed to cannabis compared with non-exposed individuals. Forest plot of study-specific risk ratios (RRs) and pooled random-effects estimate (Mantel–Haenszel method). Square size is proportional to study weight; horizontal lines indicate 95% confidence intervals; and the diamond represents the pooled estimate.

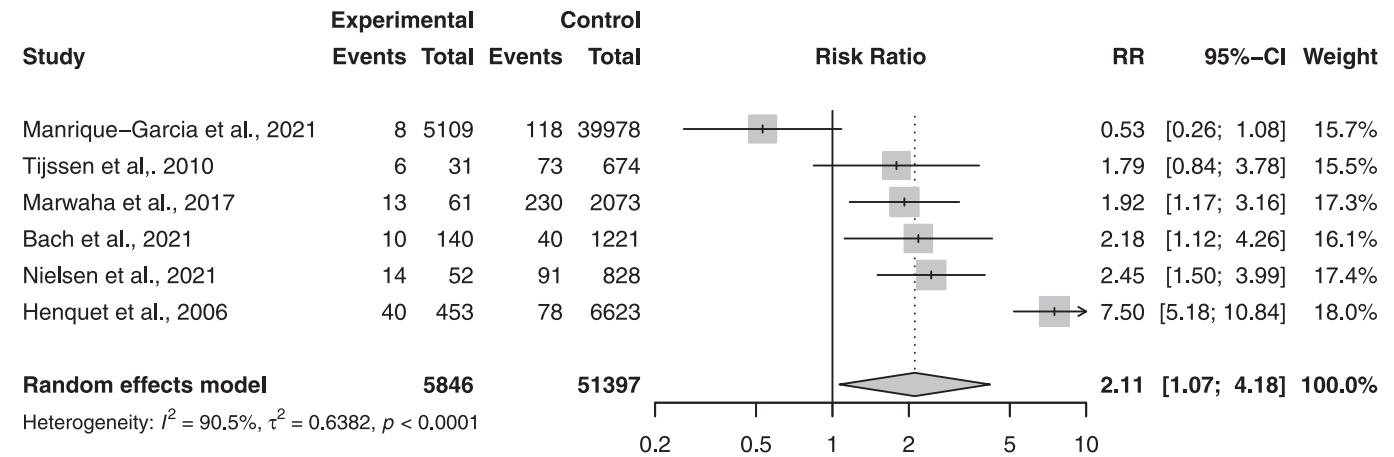


Fig. 3. Risk of incident manic and hypomanic symptoms among individuals exposed to cannabis compared with non-exposed individuals. Forest plot of study-specific RRs and pooled random-effects estimate (Mantel–Haenszel method). Square size is proportional to study weight; horizontal lines indicate 95% confidence intervals; and the diamond represents the pooled estimate.

3.5. Sensitivity analyses

Leave-one-out sensitivity analyses are reported in eFigure 3 and eFigure 4. For BD, the pooled estimate remained statistically significant across all iterations, with RR ranging from 2.36 to 2.82, suggesting that the finding was robust to the exclusion of individual studies. Heterogeneity remained moderate to high across iterations ($I^2 = 64.6\%$ – 85.8%).

For mania/hypomania, the pooled estimates remained above 1 across all iterations, but statistical significance was lost after exclusion of several individual studies (Bach et al., 2021; Henquet et al., 2006; Marwaha et al., 2018; Nielsen et al., 2021; Tijssen et al., 2010). RR ranged from 1.62 to 2.78, and heterogeneity remained high ($I^2 = 69.4\%$ – 92.3%), indicating that this result was less stable and more sensitive to the influence of individual studies.

In subgroup analyses for BD outcome, pooled estimates were numerically similar for studies defining exposure as CUD ($k = 2$; $RR = 2.35$, 95% CI 2.09–2.64) and for studies using non-CUD cannabis use definitions ($k = 6$; $RR = 2.56$, 95% CI 1.44–4.53), with no significant subgroup differences ($p = 0.77$). Similarly, in subgroup analyses by age group (mean sample age at baseline ≤ 18 vs > 18 years), pooled estimates

were comparable between studies with a mean age > 18 years ($k = 5$; $RR = 2.57$, 95% CI 1.22–5.41) and those with a mean age ≤ 18 years ($k = 3$; $RR = 2.27$, 95% CI 1.48–3.50), with no significant subgroup difference ($p = 0.78$).

On the other hand, analyses by follow-up duration suggested stronger associations in studies with shorter follow-up (≤ 3 years; $RR = 3.34$, 95% CI 2.03–5.50) than in those with longer follow-up (> 3 years; $RR = 1.50$, 95% CI 0.95–2.37), although the longer follow-up estimate was not statistically significant (between-subgroup differences $p = 0.0206$) (eTable 5).

Subgroup analyses for manic/hypomanic outcomes by age group (mean sample age ≤ 18 vs > 18 years) showed no evidence of between-subgroup differences ($p = 0.9976$). The pooled association was statistically significant in studies with mean age ≤ 18 years ($RR = 2.10$, 95% CI 1.53–2.88) but not in studies with mean age > 18 years ($RR = 2.11$, 95% CI 0.47–9.50); (eTable 6).

Meta-regression analyses for BD outcomes are presented in eTable 7. Publication year significantly moderated the pooled effect, with more recent studies tending to report smaller effect estimates ($k = 8$; $\beta = -0.0780$ per year; $p = 0.0242$). Both older mean sample age ($k = 6$; $\beta = 0.0638$ per 1-year increase; $p = 0.0529$) and shorter follow-up duration

($k = 8$; $\beta = -0.0317$ per year; $p = 0.0576$) showed trend-level associations with larger pooled effects. The proportion of females and study quality did not significantly moderate the results (all $p > 0.05$).

For manic/hypomanic symptom outcomes, meta-regression analyses are presented in eTable 8. Longer follow-up duration ($k = 6$; $\beta = -0.0598$ per year; $p = 0.0064$), a higher proportion of females ($k = 6$; $\beta = 0.0271$; $p = 0.0497$), and older mean age ($k = 6$; $\beta = 0.0598$ per 1-year increase; $p = 0.0296$) were significantly associated with the pooled effect. Year of publication showed a non-significant trend, with more recent studies tending to report smaller pooled effects ($k = 6$; $\beta = -0.0862$ per year; $p = 0.0669$). Cannabis-use frequency (weekly vs. lifetime) and study quality were not significantly associated with the pooled effect (all $k = 6$; $p > 0.05$).

3.6. Quality assessment

16 studies (84.2%) were rated as good quality (NOS 7–9) and 3 studies (15.4%) as moderate quality (NOS 4–6). NOS scores ranged from 6 to 9 (mean 8.0, median 8), with no studies rated as poor quality. Domain-level summaries are reported in eFigure 5.

4. Discussion

The present systematic review and meta-analysis is to our knowledge, the first to synthesise longitudinal evidence on the association between cannabis use and subsequent bipolar-spectrum outcomes. Across studies, cannabis use was associated with a two-and-a-half-fold higher risk of subsequent BD and an approximately two-fold higher risk of manic/hypomanic symptoms compared with non-use. By focusing specifically on longitudinal studies in which cannabis exposure was measured before incident manic symptoms or first bipolar diagnosis, the findings provide evidence of temporal precedence between measured cannabis exposure and subsequent bipolar-spectrum outcomes, although they do not establish that cannabis exposure preceded the underlying illness process (Kuhns et al., 2022).

Overall, our findings indicate that cannabis use prospectively confers a substantially elevated risk for bipolar-spectrum outcomes. Importantly, our synthesis includes eight studies contributing to the incident BD meta-analysis, thus expanding the longitudinal evidence base, which previously relied on only two to four studies (Henquet et al., 2006; Marwaha et al., 2018; Tjissen et al., 2010; van Laar et al., 2007). Gibbs et al. reported a pooled odds ratio of 2.97 (95% CI: 1.80–4.90) for the association between cannabis use and incident manic symptoms in only two longitudinal studies (Gibbs et al., 2015), which points in the same direction as our findings for incident manic/hypomanic symptoms. In contrast, a quantitative synthesis by Maggu et al. pooled four longitudinal studies under a bipolar-spectrum framework without consistently separating incident BD from manic/hypomanic symptom outcomes (Maggu et al., 2023), limiting direct comparison with our disorder-specific meta-analysis.

Within our review, moderator and sensitivity analyses indicated substantial between-study heterogeneity. Subgroup analyses provided no evidence that the association with incident BD differed by exposure definition (CUD vs. non-CUD/lifetime use) or by age group (adolescents/young adults vs adults/older samples). The absence of evidence for differences between age-defined subgroups suggests that the association was not restricted to predominantly adolescent or adult samples. However, given the limited number of studies, this finding should be interpreted cautiously. In contrast, follow-up duration appeared to influence estimates ($p = 0.0206$) with stronger associations in studies with shorter follow-up. Given the diagnostic delay in bipolar disorder (Moreno et al., 2007; UK, 2025) and the limited number of studies available for regression analyses, this finding should be considered exploratory and interpreted cautiously, as it may be influenced by individual studies and between-study differences in case ascertainment or timing of outcome detection. At the individual-study level, van Laar

et al. (van Laar et al., 2007) reported a substantially larger effect estimate than most other included studies (RR 9.34, 95% CI 4.42–19.75). This study used a 3-year follow-up, defined cannabis exposure as lifetime use on more than five occasions and assessed bipolar disorder using the DSM-III-R/CIDI 1.1 framework. Its relatively short follow-up and larger effect estimate illustrate how individual study characteristics may contribute to the apparent association between follow-up duration and effect size, although they cannot establish that follow-up duration itself accounts for this variability. However, the leave-one-out analysis indicated that the overall association remained robust after excluding this study (RR 2.06, 95% CI 1.47–2.88), although heterogeneity remained substantial ($I^2 = 78.7\%$). Thus, no single study appeared to fully account for the observed heterogeneity.

However, for manic/hypomanic outcomes, the evidence was less stable: moderator findings were difficult to interpret, and pooled estimates were more sensitive to the exclusion of individual studies. Alternatively, longer follow-up periods may increase exposure misclassification, as a greater proportion of participants may discontinue cannabis use over time, potentially attenuating observed associations. Overall, these analyses are more informative about sources of uncertainty in the evidence base than about any single moderator-driven explanation of risk (Higgins et al., 2024).

To place these findings in a wider context, the broader literature on psychotic disorders provides an informative point of comparison. A recent meta-analysis reported that cannabis use was associated with incident psychotic disorders with a pooled relative risk of 3.19, with even larger estimates in unadjusted analyses (Burke et al., 2024). Earlier meta-analytic work likewise found an approximately two-fold increase in risk for psychotic outcomes among for average cannabis compared with non-users (Marconi et al., 2016). Although these estimates are not directly comparable because of differences in outcomes and study designs, our pooled estimate for BD (RR 2.46) falls between risks previously reported in meta-analyses for psychotic disorders (RR 2.00; 3.19). This may be biologically plausible given the partial overlap between psychotic and bipolar-spectrum disorders in dopaminergic signalling and frontostriatal and cortico-limbic dysfunction, suggesting that cannabis may increase risk through partly shared vulnerability pathways (Diwadkar et al., 2014; McIntosh et al., 2008; Qi et al., 2022). Recent longitudinal evidence showing that cannabis-induced psychosis may subsequently be followed by either schizophrenia-spectrum or bipolar disorder diagnoses further supports the possibility of divergent clinical trajectories following cannabis-related neuropsychiatric presentations (Javed et al., 2026).

One pathway through which cannabis may influence frontostriatal and cortico-limbic systems is via THC effects on endocannabinoid-sensitive circuits involved in mood and reward processing. Tetrahydrocannabinol (THC) acts primarily through CB1 receptors (Schurman et al., 2020), which are densely expressed in frontostriatal and cortico-limbic circuits implicated in reward processing and affect regulation (Haber and Knutson, 2010; Katona and Freund, 2012). By modulating inhibitory GABAergic transmission, cannabis exposure may alter excitation–inhibition balance and indirectly influence dopaminergic signalling within networks central to mood stability (Chou et al., 2022). This dopaminergic dysregulation is also consistent with emerging neurobiological markers of altered dopamine function in cannabis users, including neuromelanin-sensitive imaging findings indicating increased signal in individuals with cannabis use disorder and psychosis, supporting convergence on dopaminergic pathways (Ahrens et al., 2025).

Although these shared dopaminergic and frontostriatal mechanisms may account for part of the neurobiological effects of cannabis across psychotic and bipolar-spectrum outcomes, they may not fully explain the divergent clinical trajectories observed across disorders. Although bipolar disorder remains comparatively understudied within this literature (Olivier et al., 2025), mechanisms related to affective regulation and reward sensitivity may provide an additional explanation for manic-spectrum outcomes. The reward hypersensitivity model of bipolar

disorder provides a complementary framework, positing heightened responsivity of frontostriatal reward systems (Alloy and Nusslock, 2019). In individuals with elevated baseline reward sensitivity, exogenous modulation of dopaminergic signalling via cannabis exposure could plausibly amplify approach motivation and affective reactivity, increasing the likelihood of manic-spectrum outcomes (Bossong et al., 2015). Cannabis exposure may also affect broader biological systems, including neural function, mitochondrial biology, inflammatory pathways, lipid metabolism, and the endocannabinoid system; however, these mechanisms may converge on shared neurobiological processes (Delgado-Sequera et al., 2024).

While these mechanisms provide a biologically plausible framework, alternative and complementary explanations should also be considered. Reverse causation cannot be excluded, whereby individuals with emerging affective instability or prodromal symptoms, such as sleep disturbance or mood instability, may be more likely to initiate or increase cannabis use, including as a form of self-medication (Hasler et al., 2022; Miranda et al., 2024). Thus, although the longitudinal design establishes that the measured cannabis exposure preceded the subsequent measured outcome, it cannot exclude the possibility that cannabis use emerged in response to an underlying illness process that preceded the formal diagnosis or onset captured by the included studies. In addition, genetic liability may contribute independently to risk. Large-scale studies suggest that both polygenic risk and cannabis use exert additive effects on the likelihood of psychotic disorders, supporting a model of shared vulnerability rather than a purely causal relationship (Austin-Zimmerman et al., 2024). Although this evidence derives primarily from psychosis research, the extent to which these mechanisms operate similarly in bipolar disorder remains less well established.

Clinically, our findings suggest that cannabis use should be considered a potentially relevant marker of risk in young people presenting with emerging bipolar-spectrum features. It is known that many individuals who later develop BD have prior contact with mental health services, highlighting opportunities for early identification and intervention (Aymerich et al., 2025; Lang et al., 2022). In this context, services seeing adolescents and young adults with affective lability, subthreshold manic symptoms, recurrent depressive presentations, or a family history of bipolar disorder should actively assess and monitor cannabis exposure as part of clinical formulation and follow-up (Pfennig et al., 2017; Saraf et al., 2021). More broadly, these findings support discussing cannabis use openly with patients and caregivers, including the potential risk for bipolar-spectrum outcomes, and offering support for reduction or cessation as well as management of co-occurring substance use (Goldstein et al., 2014; Quick et al., 2022).

From a public health perspective, the results strengthen the rationale for prevention strategies aimed at delaying initiation and reducing heavy use during adolescence (Fischer et al., 2022), a developmental period during which endocannabinoid signalling plays a critical role in brain maturation. These findings also have implications at the policy level, supporting clear public health messaging on the potential risks associated with cannabis use, harm reduction approaches, and regulatory measures to reduce exposure among clinically vulnerable populations (Cséte et al., 2016; Hall et al., 2019). This may be particularly relevant in settings where recreational cannabis legalisation may increase youth exposure (Hall and Lynskey, 2020; Pawar et al., 2024).

Future research should prioritize longitudinal designs with harmonized measures of cannabis exposure as current evidence used in this work, is often based on binary or heterogeneous definitions of use (Moore et al., 2007). Additional studies are warranted to examine age of initiation and developmental timing effects, particularly during adolescence, as well as potential neurobiological mechanisms linking cannabis exposure to bipolar-spectrum outcomes (Kuhns et al., 2022). In addition, genetically informed and other quasi-experimental approaches may help disentangle shared liability from potentially causal effects (Cheng et al., 2023; Treur et al., 2021).

4.1. Limitations

Our study has some limitations that should be acknowledged. First, although inclusion was restricted to longitudinal studies to strengthen temporal inference, the evidence base remains observational, limiting causal inference. Second, the meta-analysis relied on crude risk ratios, which limited the ability to account consistently for key confounders such as tobacco, alcohol, and other substance use, particularly given the heterogeneity in adjustment across primary studies. Third, substantial between-study heterogeneity likely reflects genuine differences in baseline risk, follow-up duration, and variability in exposure and outcome definitions. For instance, cannabis exposure was frequently self-reported and inconsistently characterized, with limited information on age at initiation, frequency, potency, persistence, and change over time. Fourth, although prior evidence supports a dose-response relationship between cannabis use and psychosis (Marconi et al., 2016), the available data did not allow us to examine dose-response effects in the present meta-analysis. In addition, the increasing potency of cannabis products in many countries may influence risk estimates, and future studies capturing detailed exposure metrics will be important to better characterise these associations. Finally, statistical power was limited for several secondary analyses. Because meta-regressions were based on only six to eight studies, they had limited power to detect moderator effects. For the same reason, publication-bias assessments were also underpowered, and any apparent absence of small-study effects should be interpreted cautiously.

5. Conclusion

Cannabis use is associated with an increased risk of subsequent bipolar-spectrum outcomes in people without previous bipolar disorder. While these findings cannot be interpreted as proof of direct causality, they support considering cannabis exposure as a clinically relevant factor in the assessment of young people with emerging affective symptoms. Routine evaluation of cannabis use and monitoring of bipolar disorder outcomes, together with prevention strategies focused on delaying initiation and reducing frequent use, is therefore warranted. Future longitudinal studies should clarify developmental timing, dose-response relationships, and mechanisms underlying this association.

CRediT authorship contribution statement

Cecilia Sanjuan-Ortiz: Writing – original draft, Visualization, Methodology, Formal analysis, Data curation, Conceptualization. **Paula Querol:** Writing – original draft, Methodology, Formal analysis, Data curation, Conceptualization. **Claudia Aymerich:** Writing – review & editing, Validation, Methodology, Formal analysis. **Nuria Laherran:** Writing – review & editing. **Fanny Ditlevsen:** Writing – review & editing. **Pablo Navalón:** Writing – review & editing. **Luis M. Rojo-Bofill:** Writing – review & editing. **Allan H. Young:** Writing – review & editing. **Celso Arango:** Writing – review & editing. **Aditya Sharma:** Writing – review & editing. **Marta Di Forti:** Writing – review & editing. **Robin M. Murray:** Writing – review & editing. **Christoph U. Correll:** Writing – review & editing. **Gonzalo Salazar de Pablo:** Writing – review & editing, Supervision, Project administration, Methodology, Conceptualization.

Declaration of Generative AI and AI-assisted technologies in the writing process

The authors used ChatGPT (OpenAI) and Claude, solely to assist with language editing and improvement of readability. All scientific content, interpretation of results, and conclusions were developed and verified by the authors, who take full responsibility for the content of this manuscript.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jad.2026.122588>.

Data availability

Data sharing is not applicable as no new datasets were generated. Further data extracted from the included studies are available from the corresponding author upon reasonable request.

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