Prenatal cannabis exposure and the risk for neuropsychiatric anomalies in the offspring: a systematic review and meta-analysis

Hely Bassalov, PharmD*; Noa Yakirevich-Amir, MD*; Inbal Reuveni, MD; Catherine Monk, PhD; Sharon Florentin, MD; Omer Bonne, MD**; Ilan Matok, PhD**

OBJECTIVE: To evaluate the association between cannabis use during pregnancy and the risk for long-term neuropsychiatric pathology in the offspring.

DATA SOURCES: MEDLINE, EMBASE, and Cochrane library databases were systematically searched until January 22, 2024, with no language or date restrictions.

STUDY ELIGIBILITY CRITERIA: Studies were eligible for inclusion if they reported quantitative data on any long-term neuropsychiatric outcome in offspring whose mothers used cannabis during pregnancy for medical or recreational use, by any route and at any trimester, in comparison to offspring of women who abstained from cannabis use during pregnancy. All observational study designs were included in the analysis.

STUDY APPRAISAL AND SYNTHESIS METHODS: A systematic review and meta-analysis were performed according to the PRISMA and MOOSE guidelines. The data was extracted independently by 2 reviewers. The following offspring outcomes were of interest: attention-deficit/hyperactivity disorder (ADHD), autism spectrum disorder (ASD), depression, anxiety, psychotic disorders, as well as cannabis and other substance use. Odds ratios (OR) and 95% confidence intervals (CI) were pooled for each neuropsychiatric outcome in the offspring of women exposed to cannabis during pregnancy compared with nonexposed. Data were pooled using random-effects models.

RESULTS: Eighteen eligible observational studies were included in the systematic review, and 17 were included in the final quantitative analysis, representing 534,445 participants. After adjusting for confounders, the pooled OR for ADHD was 1.13 (95% CI 1.01—1.26); for ASD, the pooled OR was 1.04 (95% CI 0.74—1.46); for psychotic symptoms, the pooled OR was 1.29 (95% CI 0.97—1.72); for anxiety, the pooled OR was 1.34 (95% CI 0.79—2.29); for depression, the pooled OR was 0.72 (95% CI 0.11—4.57); and for offspring's cannabis use, the pooled OR was 1.20 (95% CI 1.01—1.42).

CONCLUSION: Prenatal cannabis exposure is not associated with an increased risk of ASD, psychotic symptoms, anxiety, or depression in offspring. However, it may slightly elevate the risk of ADHD and predispose offspring to cannabis consumption. Despite these findings, caution is warranted regarding cannabis use during pregnancy. Further research is imperative, especially given the increasing potency of cannabis in recent years.Video:

Key words: anxiety, attention-deficit/hyperactivity disorder, autism spectrum disorder, depression, long-term outcomes, maternal cannabis use, mental health, neurodevelopment, neuropsychiatry, offspring health, psychotic symptoms, substance use

From the Department of Clinical Pharmacy, School of Pharmacy, Faculty of Medicine, Hebrew University of Jerusalem, Jerusalem, Israel (Bassalov and Matok); Department of Psychiatry, Hadassah Medical Center, Jerusalem, Israel (Yakirevich-Amir, Reuveni, Florentin, and Bonne); Department of Obstetrics and Gynecology, Vagelos College of Physicians and Surgeons, Columbia University Irving Medical Center, New York, NY (Monk); and New York State Psychiatric Institute, New York, NY (Monk).

*H.B. and N.Y.-A. contributed equally to this work.

**O.B. and I.M contributed equally in directing this study.

Received March 2, 2024; revised June 4, 2024; accepted June 14, 2024.

The authors report no conflict of interest.

The authors received no funding or support for conducting this study.

PROSPERO registration date: May 24th, 2021.

PROSPERO registration number: CRD42021252601.

This study's findings were presented at the following meetings. The 34th annual conference of the European Network of Teratology Information Services (ENTIS), Dublin, Ireland, Aug. 31st—Sept. 2nd, 2023. European Society for Developmental, Perinatal and Pediatric Pharmacology (ESDPPP) Congress, Prague, Czech Republic, June 28—30, 2023. The third Annual Conference of Clinical Pharmacy, Kfar Blum, Israel, June 15—17, 2023. The 26th Annual Conference of the Israel Society of Biological Psychiatry, Kfar Blum, Israel, March 28—30, 2023.

Corresponding author: Ilan Matok. ilan.matok@mail.huji.ac.il

0002-9378/$36.00 • • https://doi.org/10.1016/j.ajog.2024.06.014

Click Supplemental Materials and Video under article title in Contents at ajog.org

AJOG at a Glance

Why was this study conducted?

The prevalence of cannabis use among pregnant women is increasing significantly, in line with the global trend toward cannabis legalization. Given that Δ9-tetrahydrocannabinol, the primary psychoactive compound in cannabis, can easily cross the placenta and potentially impact the developing fetal brain, investigating the potential risks associated with prenatal cannabis use on the long-term neuropsychiatric health of offspring is crucial.

Key findings

A systematic review and meta-analysis comprising over 500,000 participants found no significant association between prenatal cannabis exposure and the risk of autism spectrum disorder, psychotic symptoms, anxiety, or depression in offspring. Prenatal cannabis exposure was associated with a slight increase in the risk of attention-deficit/hyperactivity disorder and heightened vulnerability to cannabis consumption in offspring.

What does this add to what is known?

While most neuropsychiatric anomalies showed no significant association with prenatal cannabis exposure, the subtle increase in attention-deficit/hyperactivity disorder risk suggests the need for ongoing exploration of the impact of prenatal cannabis use on long-term offspring's neurodevelopment.

Introduction

Cannabis is increasingly used for recreational and medicinal purposes in the general population.[1] The recommendations published by the American College of Obstetricians and Gynecologists[2] and the American Academy of Pediatrics[3] state that any medical and recreational cannabis consumption in preconception, pregnancy, or lactation should be discouraged. However, cannabis use by pregnant women is increasing significantly, in parallel with the growing global trend of cannabis legalization.[4–7] A large-scale representative survey in the United States reported approximately a 2-fold increase in the prevalence of past-month cannabis use among pregnant women from 2002 to 2017.[6] In states where medical and nonmedical cannabis use is legalized, an even greater increase in its use was observed.[8,9]

Many women state that cannabis is relatively "natural" and safe during pregnancy compared to other substances, including prescription medication.[10] According to the Pregnancy Risk Assessment Monitoring System report, the most frequently reported reasons for cannabis use during pregnancy were to relieve stress or anxiety, nausea or vomiting, pain, and for recreational purposes.[11]

The primary psychoactive ingredient of cannabis, Δ9-tetrahydrocannabinol (Δ9-THC), is a small and highly lipophilic molecule. Thus, it easily crosses the placenta and rapidly distributes to the fetal brain.[12] In humans, the endocannabinoid system is already expressed at an early stage of fetal development, and it is important to the development of various brain structures associated with mood, cognition, and reward.[13]

Human and animal studies showed that prenatal cannabis exposure may cause dysregulation of dopamine receptor D2 in the fetal brain, which may result in unfavorable neuropsychiatric outcomes and increased susceptibility to drug addiction in the offspring.[14,15] Additional animal studies showed that prenatal cannabis exposure changes dopamine activity in brain areas associated with attention deficits and hyperactivity disorders.[16] Animal studies also indicate that maternal Δ9-THC exposure disrupts serotonergic transmission by reducing serotonin levels in various brain regions in the offspring, potentially contributing to mood dysregulation and elevating the risk of depression in the offspring.[13]

Several human studies examined the possible impact of prenatal cannabis exposure on children's cognition, behavior, and neuropsychiatric development.[17–19] However, observational studies examining the long-term risks of prenatal cannabis exposure differ widely in the extent and timing of cannabis exposure, the duration of follow-up, and the methods used to evaluate outcomes.[20] This variability makes it difficult to understand the potential harm of in-utero cannabis exposure fully.

Considering the rising rates of cannabis use among reproductive-age women, there is an urgent need to investigate the possible risks related to cannabis consumption during pregnancy on the long-term morbidity of the offspring. Therefore, we performed a systematic review and meta-analysis to determine the association between prenatal cannabis exposure and the risk for neuropsychiatric pathology in the offspring.

Objectives

The main goal of this research is to thoroughly evaluate the long-term neuropsychiatric safety of cannabis exposure during pregnancy by comprehensively analyzing the existing body of evidence on this subject. We hypothesized that prenatal cannabis exposure increases the risk of neurodevelopmental and psychiatric complications in the offspring.

Methods

Data sources and search strategy

The systematic review was conducted according to the framework guidelines of Preferred Reporting Items for Systematic Reviews and Meta-Analysis (Appendix A) and the Meta-analysis of Observational Studies in Epidemiology reporting guidelines (Appendix B). A systematic search was conducted in MEDLINE, EMBASE, and Cochrane library databases up to January 22, 2024, without language or date restrictions. The search

was performed using the following combinations of keywords: "cannabis," "marijuana," "THC," "CBD," "pregnancy," "prenatal," "neurodevelopment," "autism spectrum disorder," "attention deficit hyperactive disorder," "mental," "psych," "offspring," "child," "long term." Additionally, we manually screened the reference lists of selected reviews and eligible studies to ensure that all relevant studies were identified. The study protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO) in May 2021 (CRD42021252601). The study did not require approval from an institutional review board.

Eligibility criteria

Studies were eligible for inclusion if they reported quantitative data on any long-term neuropsychiatric outcome in offspring whose mothers used cannabis during pregnancy for medical or recreational use, by any route, at any trimester, compared to offspring who were not exposed to cannabis during pregnancy.

The following offspring outcomes were of interest: attention-deficit/hyperactivity disorder (ADHD), autism spectrum disorder (ASD), depression, anxiety, psychotic disorders, as well as cannabis and other substance use (cigarette smoking, illicit drug use). We excluded studies reporting only isolated ADHD symptoms, such as attention problems, hyperactivity, or impulsivity and included only manuscripts providing a comprehensive evaluation of ADHD, such as ADHD diagnosis or ADHD reported by the Diagnostic and Statistical Manual of Mental Disorders—oriented scales. This decision was taken due to enormous variability in the methods used to evaluate isolated symptoms, as opposed to the evaluation of the complete ADHD entity, which was our main outcome of interest. Studies reporting on internalizing problems or mixed expressions of anxiety/depressive symptoms were also excluded, as we were interested in analyzing each of these psychiatric outcomes separately.

All observational study designs were included in the analysis. Case reports, case series, guidelines, expert opinions, editorials, reviews, letters to the author, comments, and animal studies were excluded. Outcomes reported from the same cohort in different publications were included only once in each analysis. Studies that reported concomitant use of cannabis with tobacco, alcohol, or other illicit drugs, without separate analysis for cannabis exposure only, were excluded to minimize the effect of confounding.

Study selection

Data were screened for eligibility and extracted independently by 2 reviewers (N.Y.A and H.B). After removing duplicates, the relevant papers were screened by title and abstracts against the inclusion criteria. The 2 reviewers were blinded to each other's decisions. Disagreements were resolved through consensus or consultation with a third reviewer (I.M.). Afterward, the relevant full papers were evaluated by methods and outcomes.

Data extraction

The following data were extracted from eligible studies: study details (authors, study design, country, year), participant details (number of cannabis exposed and nonexposed, trimester of exposure), exposure details (cannabis use indication-medical or recreational, exposure assessment method, type of cannabis, dose or intensity, frequency of cannabis use, route of administration), length of follow-up, outcomes in the offspring, outcomes measurement method, and adjustments made for confounding variables. Outcome estimates were extracted as hazard ratios, risk ratios (RR), odds ratios (OR), incidence rate ratios, mean difference, means with standard deviations, r regression coefficients, or β regression coefficients. In cases where relevant information was missing for our analysis, the authors of the included studies were contacted to provide us with additional requested data.

Risk of bias assessment

Studies' risk of bias was assessed using the Newcastle-Ottawa Scale (NOS), a tool for assessing the quality of observational studies.[21,22] Each study was rated by selection, comparability, and outcome (Appendix C). According to the total star rating each study received, the studies were classified as "high risk" (5 stars and below), "intermediate risk" (6—7 stars), or "low risk" of bias (8—9 stars). The assessments were carried out independently by the 2 reviewers. Disagreements were resolved through consensus or by consultation with a third reviewer.

Data synthesis and statistical analysis

The prevalence of prenatal cannabis use was calculated by dividing the number of offspring exposed to cannabis prenatally by the total sample size within each study. Additionally, the overall pooled prevalence of cannabis use during pregnancy was evaluated. To prevent data duplication from studies reporting various outcomes from the same cohort, we ensured each cohort was represented only once in the pooled analysis. This was achieved by including the study with the largest participant count from each cohort.

A meta-analysis was conducted on neuropsychiatric outcome estimates reported in at least 2 studies: ADHD, ASD, psychotic symptoms, anxiety, depression, and cannabis use. As no sufficient studies were found examining the link between prenatal cannabis exposure and offspring substance use beyond cannabis, the outcome for other substance use was not analyzed. A random effects meta-analysis was used to pool the results. This model assumes that the effect size varies across studies due to differences in study designs, study populations, level of drug exposure, outcome measurements, and length of follow-up.[23,24] We pooled the ORs and 95% confidence intervals (CI) for each neuropsychiatric outcome in offspring prenatally exposed to cannabis compared with nonexposed. In cases where the effect size was reported as a regression coefficient, we first converted it to OR by exponentiation before performing the pooled analysis.[25] Moreover, we approximated RRs to ORs under the assumption that the reported outcomes

are rare, with a prevalence of the outcomes being less than 10%.[26–28]

For the main analysis, we pooled fully adjusted effect size estimates, as reported in each study. For the ADHD, ASD, anxiety, and psychotic symptoms outcomes, we performed analyses using crude effect size estimates to assess the potential influence of confounding variables on the association between prenatal cannabis exposure and neuropsychiatric anomalies (Appendix D). Heterogeneity was measured by Q statistics and I^2 statistics. I^2 reflects the percentage of variation across studies' estimates attributed to the heterogeneity between the studies rather than sampling error.[29] I^2 values of 25%, 50%, and 75% indicate low, intermediate, and high heterogeneity, respectively.[30] Statistical significance in the heterogeneity test was defined as a P-value $<.1$. The results are presented as forest plots for a graphic summary. Additionally, 95% prediction intervals (PI) were calculated for neuropsychiatric outcomes reported in at least 3 studies: ASD, psychotic symptoms, and anxiety. A PI estimates the range within which the true effect of a future study is likely to fall, incorporating both within-study and between-study variability.[31] For ADHD, the PI is not displayed due to an estimated between-study variance of zero.

Sensitivity analyses were conducted to assess the impact of variations in offspring age across studies on the overall effect size estimates. This was done by excluding studies that exhibited substantial deviations in offspring age ranges compared to the other studies within each outcome. The results of these sensitivity analyses were compared to the main analysis to evaluate any differences in effect size estimates.

All analyses and graphical visualization were performed using Comprehensive Meta-analysis software. Statistical significance in pooled analysis was defined as a P-value $<.05$.

Results

Study selection

Figure 1 represents the flow diagram of the search process we performed. Our search yielded 1935 articles, of which 67 articles underwent full-text screening. Of those, 18 studies were included in the qualitative analysis and 17 were included in the quantitative analysis, representing 534,445 participants from 14 different cohorts.

The overall pooled prevalence of prenatal cannabis use was 7.7% (95% CI: 3.0%, 18.2%). The highest prevalence of prenatal cannabis consumption was reported in the Maternal Health Practices and Child Development (MHPCD) study[32] (41.2%), while the lowest prevalence was reported in the BORN registry (0.6%).[33]

Study characteristics

Table 1 describes the characteristics of the studies included in the analysis and adjustments made for potential confounders in each study. All studies included are observational, 17 are cohort studies, and one is a nested case-control study.[43] In most studies, prenatal cannabis use was evaluated by maternal self-report. In only 3 studies, prenatal cannabis exposure was also assessed by maternal urine screen.[39,42,46] Seven studies evaluated prenatal cannabis exposure during all pregnancy periods,[32,33,36,43,44,48,49] 3 studies reported cannabis use in the first trimester only,[37–39] 1 study reported cannabis use in the second trimester,[46] and the remaining 7 studies did not mention the specific pregnancy stage when cannabis exposure was evaluated.[34,35,40–42,45,47] Neither of the studies reported maternal cannabis use indication.

The studies sought various symptoms, with considerable variation in the indices used for their evaluation. Table 2 describes study outcomes, classified according to the measures collected in each study.

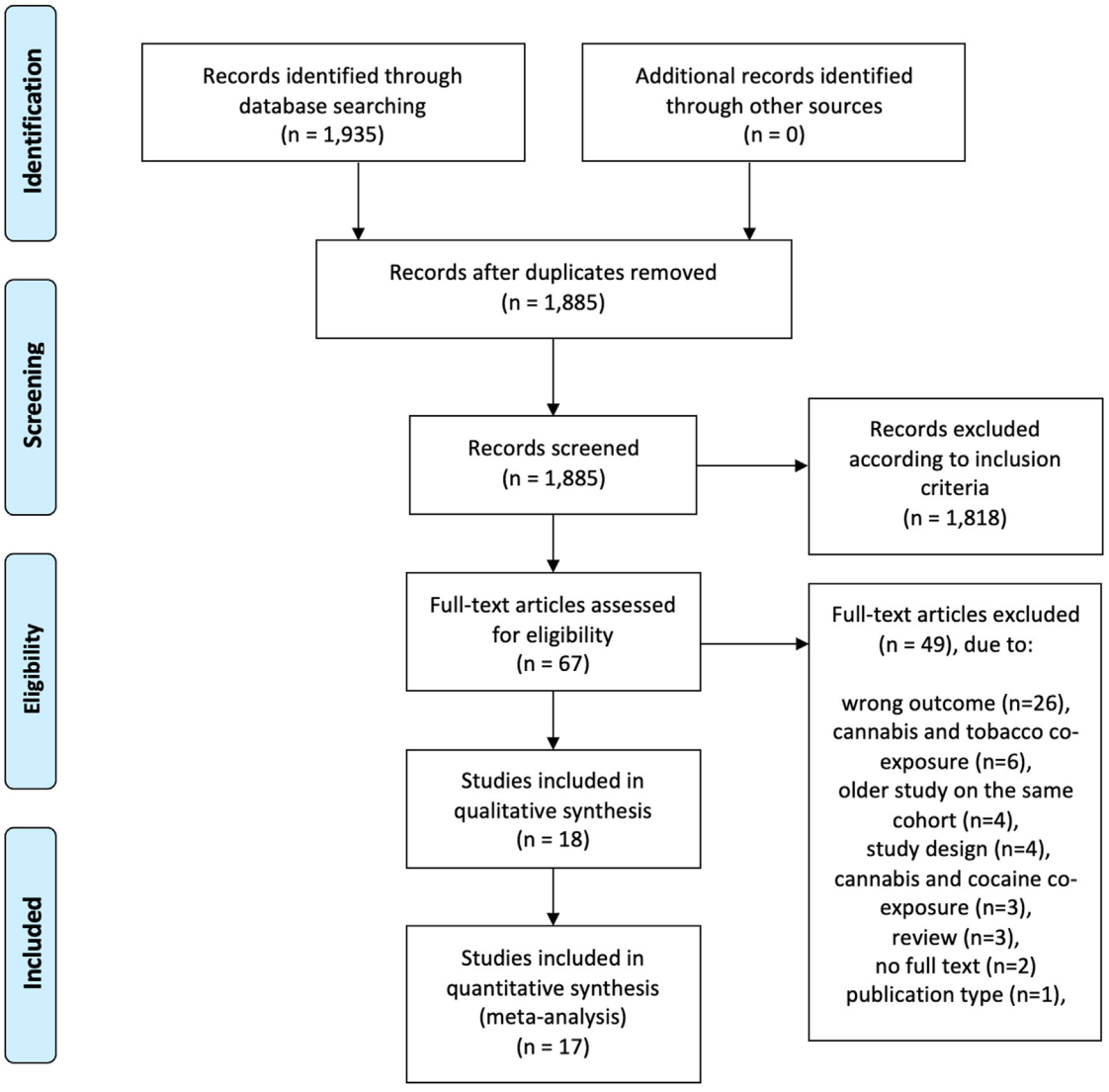
Attention-deficit/hyperactivity disorder

Six studies explored ADHD in the offspring.[33,42,44–46,48] Of these, 3 studies extracted ADHD outcomes from children's electronic medical records using diagnostic codes.[33,44,45] Two studies utilized the Child Behavior Checklist (CBCL)-ADHD scale, a screening questionnaire completed by caregivers to assess ADHD-related behaviors, using specific cut-off scores to identify clinically significant ADHD symptoms.[42,46] One study employed The Preschool Age Psychiatric Assessment (PAPA), a diagnostic interview conducted by clinical interviewers with caregivers of preschool-aged children, using diagnostic algorithms to determine ADHD presence based on observed behaviors and caregiver reports.[48] Five studies included children aged 2 to 10[33,42,45,46,48], and one included children aged 9 to 14.[44]

Autism spectrum disorder

Five studies examined ASD in the offspring,[33,43,46,47,49] employing multiple assessment methods. One study identified ASD cases through diagnostic codes in children's medical records.[33] Three studies employed ASD screening questionnaires on children's behaviors completed by mothers, such as the CBCL, the Social Communication Questionnaire, and the Modified Checklist for Autism in Toddlers, using cutoff scores to indicate ASD likelihood based on reported behaviors.[43,46,47] Two studies employed screening tools administered directly to the children, including the Autism Spectrum Quotient, a self-report questionnaire completed by the child, and the Mullen Scales of Early Learning, a cognitive assessment tool, both utilizing a threshold score to assess the likelihood of ASD traits.[43,49] Two studies also utilized confirmatory assessments for ASD: the Autism Diagnostic Observation Schedule, involving direct observation and scoring of the child's behavior and social interactions by a trained clinician, yielding standardized scores and algorithms for ASD diagnosis, and the Autism Diagnostic Interview-Revised, a structured interview conducted with caregivers, providing diagnostic algorithms based on the responses obtained.[43,47] Four studies included children between the ages 2 to 10[33,43,46,47], and one included young adults aged 19 to 20.[49]

FIGURE 1
Study flow diagram



Psychotic symptoms

Four studies assessed psychotic symptoms in the offspring.[36,37,39,40] Two studies utilized self-report questionnaires completed by children, assessing experiences like hallucinations, delusions, and disorganized thinking, with threshold scores indicating symptom presence and severity.[39,40] The remaining 2 studies employed interviews for children, conducted by clinicians or trained interviewers. One study assessed psychotic symptoms subjectively based on the clinician's judgment, while the other used specific diagnostic criteria to determine symptom presence.[36,37] Three studies included children aged 10 to 12,[36,39,40] and one included adolescents and young adults aged 16 to 21.[37]

Anxiety

Five studies evaluated anxiety in the offspring.[34,41,42,46,48] Of these, 4 studies employed parent-reported screening measures to assess anxiety symptoms in children based on parental observations of the child's behavior, such as the Conners Parent Rating Scale, Behavior Assessment System for Children, Second Edition (BASC-2), and CBCL.[34,41,42,46] These scales use threshold scores to identify clinically significant levels of anxiety based on parent responses. One study utilized the PAPA, a structured interview with caregivers, using diagnostic algorithms to determine the presence and severity of anxiety disorders based on established diagnostic criteria.[48] The studies included preschool children between the ages of 2 to 5, except for 1 study[34] that included children aged 6 to 9.

TABLE 1
Characteristics of the studies included in the analysis

Author, year	Data source	Study design	Pregnancy period	Exposed participants (unexposed)	Prenatal cannabis use prevalence	Exposure measurement method	Trimester of exposure	Outcome	Mean age of offspring at assessment (y)	Adjustments	NOS rating
O'Connell and Fried,[34] 1991	OPPS study	Cohort	1978–1983	28 (28)	50.0%	Self-report	NA	Anxiety	6–9	Maternal smoking and alcohol consumption during pregnancy, maternal age at delivery, maternal personality, and home environment	8
Porath and Fried,[35] 2005	OPPS study	Cohort	1978–1984	49 (103)	32.2%	Self-report	NA	Regular marijuana use	18	Prenatal alcohol exposure, prenatal cigarette exposure	8
Gray et al,[32] 2005	MHPCD study	Cohort	1982–1985	262 (374)	41.2%	Self-report	All trimesters	Depression	10.5	Child's IQ score, maternal current tobacco use, child's hospitalizations	7
Zammit et al,[36] 2009	ALSPAC study	Cohort	1991–1992	78 (4175)	1.8%	Self-report	All trimesters	Psychosis-like symptoms	12	Prenatal alcohol and tobacco exposure, maternal marital status during pregnancy, maternal age, financial difficulty during pregnancy, housing type, urban/rural index at birth, paternal smoking during pregnancy, maternal and paternal education, maternal use of prescribed medication (analgesics or hypnotics), maternal depression during pregnancy.	7
Day et al,[37] 2015	MHPCD study	Cohort	1982–1985	243 (353)	40.8%	SELF-report	First trimester	Psychotic symptoms	22.7	Prenatal exposure to alcohol and tobacco, gender, race, offspring use of alcohol, tobacco, and illicit drugs at 22 y, early age of onset of marijuana use.	7
Sonon et al,[38] 2015	MHPCD study	Cohort	1982–1986	242 (347)	41.1%	Self-report	First trimester	Frequency of marijuana use	22.8	Prenatal alcohol exposure in the first trimester, offspring gender, race and age at assessment	6
Bolhuis et al,[39] 2018	Generation R study	Cohort	2002–2006	85 (3123)	2.6%	Self-report; urine screen	First trimester	Psychotic-like experiences	10	Child age, child sex, child ethnicity, maternal age, maternal education level, maternal psychopathology score, maternal drinking during pregnancy.	7
Corsi et al,[33] 2020	BORN registry	Cohort	2007–2012	3148 (499,917) 3038 (494,783)	0.6%	Perinatal record	All trimesters	Autism spectrum disorder Attention-deficit/ hyperactivity disorder	1.5–10 4–10	Maternal age, income, education, preexisting maternal medical conditions, psychiatric disorders, parity, antenatal care, smoking, alcohol use, other drug use, obstetric complications, and preterm birth.	8

(continued)

TABLE 1
Characteristics of the studies included in the analysis *(continued)*

Author, year	Data source	Study design	Pregnancy period	Exposed participants (unexposed)	Prenatal cannabis use prevalence	Exposure measurement method	Trimester of exposure	Outcome	Mean age of offspring at assessment (y)	Adjustments	NOS rating
Paul et al,[40] 2021	ABCD study	Cohort	2005–2009	242 (10,834)	2.2%	Self-report	NA	Psychotic-like experiences	10	Race/ethnicity, first-degree familial history of psychopathology, prenatal exposure to tobacco or alcohol, unplanned pregnancy, prenatal vitamin use, child lifetime substance exposure, child sex, and twin or triplet status, annual household income, birthweight, maternal age at birth, gestational age when pregnancy was discovered (wk), child age, maternal educational level.	6
Rompala et al,[41] 2021	Stress in Pregnancy project	Cohort	2010–2015	68 (236)	22.4%	Self-report	NA	Anxiety Depression	3.7	Parental age, education, marital status, prenatal cigarette smoking, child's sex, age, race, maternal state/trait anxiety.	7
Murnan et al,[42] 2021	LEAF study	Cohort	2010–2016	15 (48)	23.8%	Self-report; medical record; urine screen	NA	Anxiety Attention-deficit/ hyperactivity disorder	3.5	Child's age, race, sex, prenatal tobacco exposure, household income, caregiver marital status, caregiver executive function.	7
DiGuiseppi et al,[43] 2021	SEED study	Nested case-control	2003–2011	148 (2938)	4.8%	Self-report	All trimesters	Autism spectrum disorder	4.7	Maternal education, alcohol and tobacco use during peri-pregnancy.	7
Garrison-Desany et al,[44] 2022	Boston Birth Cohort	Cohort	1998–2019	123 (3015)	3.9%	Self-report	All trimesters	Attention-deficit/ hyperactivity disorder	12	Maternal race and ethnicity, age, educational level, marital status, and pre-pregnancy body mass index, annual household income quartile, nulliparity, child sex, prenatal exposure to tobacco, alcohol, and opioids.	7
Tchuente et al,[45] 2022	Quebec Pregnancy Cohort	Cohort	1998–2003	86 (2322)	3.6%	Self-report	NA	Attention-deficit/ hyperactivity disorder	4.8	Maternal age, education level, household annual income, living alone, area of residence, race, previous children and pre-pregnancy body mass index, maternal prenatal smoking status, alcohol intake, coffee intake, cocaine use and physical activity, gestational age at delivery, maternal comorbidities, maternal depression/anxiety, maternal psychiatric disorders, maternal drug dependence expect for cannabis dependence, maternal pain, infant sex and calendar year of birth.	8

(continued)

TABLE 1
Characteristics of the studies included in the analysis *(continued)*

Author, year	Data source	Study design	Pregnancy period	Exposed participants (unexposed)	Prenatal cannabis use prevalence	Exposure measurement method	Trimester of exposure	Outcome	Mean age of offspring at assessment (y)	Adjustments	NOS rating
Moore et al,[46] 2023	Healthy Start study	Cohort	2010–2014	6 (75)	7.4%	Urine screen	Second trimester	Attention-deficit/ hyperactivity disorder Depression Anxiety Autism spectrum problems	5	Maternal age, maternal education, maternal race and ethnicity, a nonspecified maternal psychiatric diagnosis, child sex, child age at the behavioral or cognitive assessment, prenatal exposure to tobacco, and childhood exposure to tobacco.	6
Nutor et al,[47] 2023	Black American cohort	Cohort	NA	60 (112)	34.9%	Self-report; medical record	NA	Autism spectrum disorder	2	Child sex, tobacco, alcohol, and other drug exposures during pregnancy, maternal socioeconomic status.	6
Nomura et al,[48] 2023	Stress in Pregnancy study	Cohort	2010–2015	27 (123)	18.0%	Self-report	All trimesters	Anxiety Attention-deficit/ hyperactivity disorder	3.2	Child sex, child race, child ethnicity, maternal age, marital status of the parents, parity, socioeconomic status, prenatal substance use, prenatal stress, postnatal family stress, and social support at age 3.	8
Isik et al,[49] 2023	Raine study	Cohort	1989–1992	285 (2519)	10.2%	Self-report	All trimesters	Autism spectrum disorder	19–20	Maternal age, race, BMI, education, parity, maternal alcohol, cigarette, and drug use during pregnancy. paternal age, education, paternal cigarette, marijuana and drug use, family income, maternal health characteristics, maternal trauma and emotional characteristics, maternal antenatal characteristics, child sex	6

NOS, Newcastle-Ottawa Scale.

Depression

Three studies assessed depression in the offspring.[32,41,46] Of these, 2 studies employed parent-reported questionnaires to assess depressive problems in children, such as the CBCL and the BASC-2,[41,46] and 1 study used the Children's Depression Inventory, a self-report questionnaire of childhood depression.[32] All 3 methods are screening tools for depression, utilizing threshold scores to indicate the likelihood of depression based on reported behaviors or the child's responses. The studies included preschool children between the ages of 3 to 6.

Cannabis use

Two studies assessed cannabis use in the offspring.[35,38] Both studies relied on self-report measures from the offspring regarding the frequency, duration, and quantity of cannabis consumption. Additionally, urine samples were collected from the participants to validate the self-reported measures of recent cannabis use objectively. The studies included adolescents and young adults aged 16 to 22.

Risk of bias of included studies

The studies were of intermediate or low risk of bias—5 studies achieved an NOS rating of 8 stars,[33–35,45,48] 8 studies reached a score of 7 stars,[32,36,37,39,41–44] and 5 studies reached a score of 6 stars.[38,40,46,47,49] The full risk of bias assessment is provided in the supplement (Appendix C).

Meta-analysis

Attention-deficit/hyperactivity disorder

Six studies evaluated the association between prenatal cannabis exposure and ADHD in the offspring.[33,42,44–46,48] Data on this association without confounder adjustment were available in 4 studies.[33,42,44,45] A pooled analysis demonstrated that cannabis exposure during pregnancy is associated with an increased risk for ADHD ($_{crude}$OR=1.82, 95% CI: 1.16, 2.84; I^2=75%) (Figure D.1). After adjusting for relevant confounders across all 6 studies, the pooled analysis (Figure 2.) shows that the association between

TABLE 2
Classification of measurement methods as reported in each study

Outcome	Age range (y)	Evaluation method	Author
Attention-deficit/ hyperactivity disorder	2—12	Database diagnosis	Corsi et al[33]; Garrison-Desany et al[44]; Tchuente et al[45]
		The Child Behavior Checklist- ADHD; caregiver questionnaire	Murnan et al[42]; Moore et al[46]
		The Preschool Age Psychiatric Assessment (PAPA); caregiver interview	Nomura et al[48]
Autism spectrum disorder	1.5—20	Database diagnosis	Corsi et al[33]
		The Social Communication Questionnaire (SCQ); caregiver questionnaire	DiGuiseppi et al[43]
		Mullen Scales of Early Learning (MSEL); offspring behavior observation	DiGuiseppi et al[43]
		Autism Diagnostic Observation Schedule (ADOS); offspring behavior observation	DiGuiseppi et al[43]; Nutor et al[47]
		Autism Diagnostic Interview-Revised (ADI-R); caregiver interview	DiGuiseppi et al[43]
		The Child Behavior Checklist; caregiver questionnaire	Moore et al[46]; Nutor et al[47]
		The Modified Checklist for Autism in Toddlers (M-CHAT); caregiver questionnaire	Nutor et al[47]
		Autism Spectrum Quotient (AQ); offspring self-report questionnaire	Isik et al[49]
Psychotic symptoms	9—22	Psychosis-like symptoms semi-structured interview; offspring interview	Zammit et al[36]
		The Diagnostic Interview Schedule- psychosis section; offspring interview	Day et al[37]
		Youth Self Report scale; offspring self-report questionnaire	Bolhuis et al[39]
		The Prodromal Questionnaire— Brief Child Version; offspring self-report questionnaire	Paul et al[40]
Anxiety	2—9	Conners Parent Rating Scale; caregiver questionnaire	O'connell and Fried[34]
		Behavior Assessment System for Children, Second Edition (BASC-2); caregiver questionnaire	Rompala et al[41]
		The Child Behavior Checklist- anxiety; caregiver questionnaire	Murnan et al[42]; Moore et al[46]
		The Preschool Age Psychiatric Assessment (PAPA); caregiver interview	Nomura et al[48]
Depression	3—10	Children's Depression Inventory (CDI); offspring self-report questionnaire	Gray et al[32]
		Behavior Assessment System for Children, Second Edition (BASC-2); caregiver questionnaire	Rompala et al[41]
		The Child Behavior Checklist-depressive problems; caregiver questionnaire	Moore et al[46]
Regular cannabis use	16—22	Drug History Questionnaire; offspring self-report	Porath and Fried[35]
		Offspring self-report	Sonon et al[38]
		Urine screen	Porath and Fried[35]; Sonon et al[38]

cannabis exposure during pregnancy and ADHD is slightly attenuated but remained statistically significant (OR=1.13, 95% CI: 1.01, 1.26, *P*-value .04; I^2=0%). In a sensitivity analysis, the exclusion of the study by Garrison-Desany et al,[44] which included older children aged 9 to 14, did not significantly affect the overall effect size

estimate (OR=1.11, 95% CI: 0.99, 1.25, *P*-value .07; I^2=0%).

Autism spectrum disorder

Five studies evaluated the association between prenatal cannabis exposure and ASD in the offspring.[33,43,46,47,49] Data on this association without confounder adjustment were available in 3 studies.[33,43,49] A pooled analysis demonstrated that cannabis exposure during pregnancy is associated with an increased risk for ASD ($_{crude}$OR 1.45, 95% CI: 1.16, 1.80; I^2=14%) (Figure D.2). After adjusting for relevant confounders across all 5 studies, the pooled analysis (Figure 3) shows that cannabis exposure during pregnancy is not associated with an increased risk for ASD (OR=1.04, 95% CI: 0.74, 1.46, *P*-value .82; 95% PI: 0.35, 3.07; I^2=65%). In a sensitivity analysis, excluding the study by Isik et al,[49] which involved offspring aged 19 to 20, had no impact on the results (OR=1.02, 95% CI: 0.72−1.46, *P*-value .91; I^2=73%).

Psychotic symptoms

Four studies evaluated the association between prenatal cannabis exposure and psychotic symptoms in the offspring.[36,37,39,40] Data on this association without confounder adjustment were available in all 4 studies. A pooled analysis demonstrated that cannabis exposure during pregnancy is associated with an increased risk for psychotic symptoms ($_{crude}$OR=1.56, 95% CI: 1.05, 2.32; I^2=79%) (Figure D.3). After adjusting for relevant confounders, the pooled analysis (Figure 4) shows that cannabis exposure during pregnancy is not associated with an increased risk for psychotic symptoms (OR=1.29, 95% CI: 0.97, 1.72, *P*-value .08; 95% PI: 0.43, 3.89; I^2=56%). In a sensitivity analysis, when excluding the study of Day et al[37] involving adolescents and young adults aged 16 to 21, the results remained largely unchanged (OR=1.36, 95% CI: 0.85, 2.1, *P*-value .2; I^2=70%).

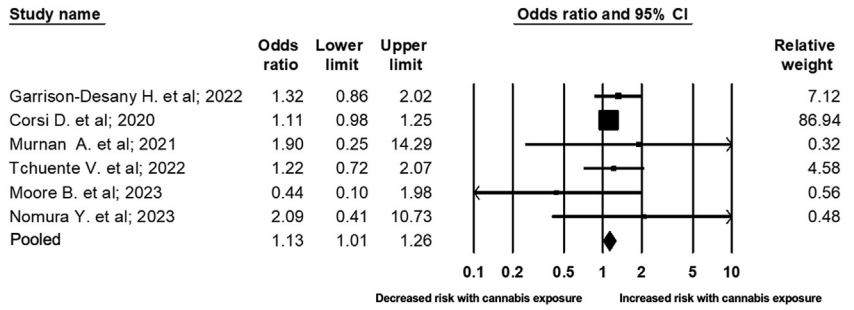
Anxiety

Five studies evaluated the association between prenatal cannabis exposure and anxiety in the offspring.[34,41,42,46,48] Data on this association without confounder adjustment were available in 3 studies.[34,41,42] A pooled analysis demonstrated that cannabis exposure during pregnancy is not associated with a significantly increased risk for anxiety ($_{crude}$OR=1.59, 95% CI: 0.75−3.38; I^2=65%) (Figure D.4). After adjusting for relevant confounders in all 5 studies, the pooled analysis (Figure 5) shows similar results (OR=1.34, 95% CI: 0.79, 2.29, *P*-value .28; 95% PI: 0.34, 5.38; I^2=32%). In a sensitivity analysis, when excluding the study by O'Connell et al,[34] which included older children than the other studies, the effect size increased but remained statistically insignificant (OR=1.58, 95% CI: 0.74, 3.39, *P*-value=.24; I^2=30%).

Depression

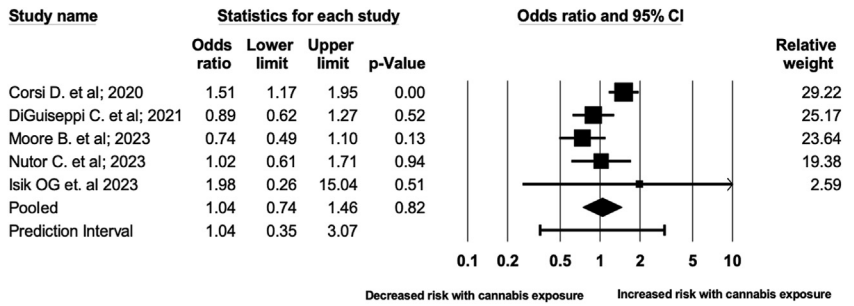
Three studies evaluated the association between prenatal cannabis exposure and depression in the offspring.[32,41,46] The study published by Gray et al[32] reported that prenatal cannabis exposure during the first and third trimesters of pregnancy, but not during the second trimester, was significantly associated with increased levels of depressive symptoms in the offspring at the age of 10 after controlling for confounding variables (β, first trimester: 1.83, *P*-value: <.01; β, third trimester 2.58, *P*-value <.01). However, we were unable to incorporate this study into the quantitative analysis due to insufficient data

FIGURE 2
Prenatal cannabis exposure and the risk for attention-deficit/hyperactivity disorder (ADHD) in the offspring



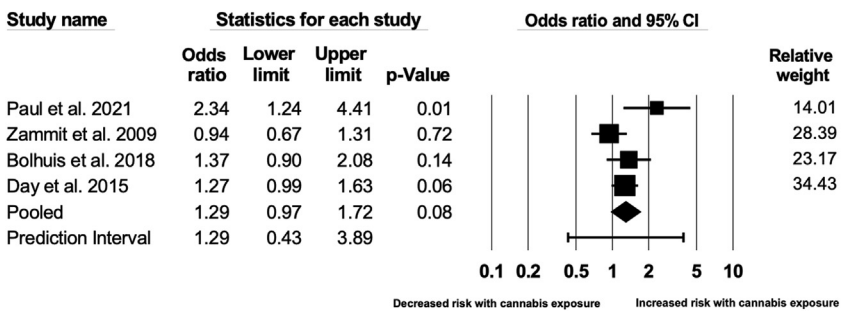
Odds ratios (OR) and 95% confidence intervals (CI) of random-effects meta-analysis of 6 studies assessing the risk for ADHD following prenatal cannabis exposure. Test for heterogeneity: χ^2: 2.989, *P*-value=.702; I^2=0%.

FIGURE 3
Prenatal cannabis exposure and the risk for autism spectrum disorder (ASD) in the offspring



Odds ratios (OR), 95% confidence intervals (CI), and 95% prediction intervals (PI) of random-effects meta-analysis of 5 studies assessing the risk for ASD following prenatal cannabis exposure. Test for heterogeneity: χ^2: 11.553, *P*-value=.021; I^2=65%.

FIGURE 4
Prenatal cannabis exposure and the risk for psychotic symptoms in the offspring



Odds ratios (OR), 95% confidence intervals (CI), and 95% prediction intervals (PI) of random-effects meta-analysis of 4 studies assessing the risk for psychotic symptoms following prenatal cannabis exposure. Test for heterogeneity: χ^2: 6.74, *P*-value=.081; I^2=56%.

provided in this study for effect size calculation. After adjusting for relevant confounders, the pooled analysis (Figure 6), without the study published by Gray et al[32] shows that cannabis exposure during pregnancy is not associated with increased risk for depression in the offspring (OR=0.72, 95% CI: 0.11, 4.57, *P*-value .73; I^2=78%).

Cannabis use

Two studies evaluated the association between prenatal cannabis exposure and regular cannabis use in young adulthood, defined as using cannabis at least once per week.[35,38] After adjusting for relevant confounders, the pooled analysis (Figure 7) shows that cannabis exposure during pregnancy is associated with a significantly increased risk for frequent cannabis use in the offspring (OR=1.20, 95% CI: 1.01, 1.42, *P*-value .03; I^2=0%).

Discussion

Principal findings

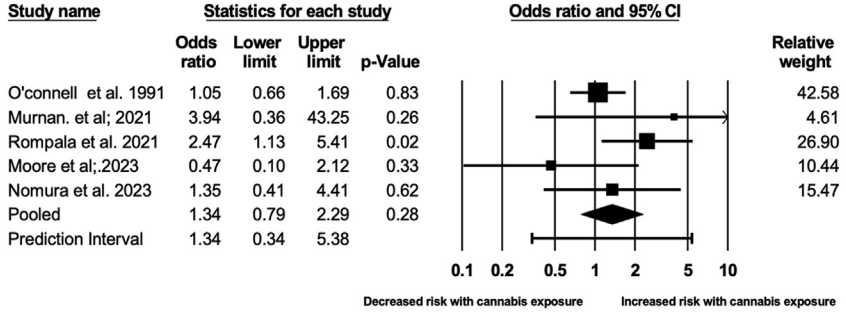
As far as we know, this is the first meta-analysis examining the association between cannabis use during pregnancy and a variety of long-term neuropsychiatric pathologies in the offspring.

Considering the accumulating knowledge of Δ9-THC transmission to the fetus, the risk for adverse neonatal birth outcomes,[50–55] and the potential psychiatric hazards associated with cannabis consumption in adolescents and adults,[56,57] our initial hypothesis was that prenatal cannabis exposure increases the risk of neurodevelopmental and psychiatric pathology in offspring. However, our hypothesis was largely unsupported, as our results indicate that prenatal cannabis exposure is not associated with an increased risk for ASD nor is it associated with the development of psychotic symptoms, anxiety, or depression. However, prenatal cannabis exposure might slightly increase the risk for ADHD and the offspring's vulnerability to consuming cannabis.

The observed disparities between crude and adjusted analyses underscore the crucial role of controlling for confounders in studies examining the effects of prenatal cannabis exposure on offspring outcomes. The attenuation of effect sizes upon confounder adjustments reveals the complex interplay of etiological factors influencing these associations. These include genetic predispositions, environmental factors, and variables like maternal age and behavior, all of which could confound the relationship between prenatal exposure and developmental outcomes. This complexity highlights the necessity for meticulous adjustment in research to isolate the specific impacts of cannabis exposure from other influencing factors.

We found a statistically significant association between prenatal cannabis exposure and a 13% increase in the risk for ADHD. While most of the individual studies included, except for the study of Moore et al,[46] demonstrated a non-statistically significant association with increased risk for ADHD, the combined effect sizes yielded sufficient statistical power to establish an overall significant association. Possible explanations for the contrasting effect size estimate reported by Moore et al[46] could be attributed to the limited number of subjects prenatally exposed to cannabis, which might be insufficient to detect an effect. Additionally, the relatively lower representation of male offspring in this study could be a factor, given that ADHD tends to be more prevalent in males.[58] Notably, the study of Corsi et al[33] significantly affected the overall pooled estimate since

FIGURE 5
Prenatal cannabis exposure and the risk for anxiety in the offspring



Odds ratios (OR), 95% confidence intervals (CI), and 95% prediction intervals (PI) of random-effects meta-analysis of 5 studies assessing the risk for anxiety following prenatal cannabis exposure. Test for heterogeneity: χ^2: 5.892, *P*-value=.207; I^2=32%.

it is the largest study, representing approximately 500,000 individuals.

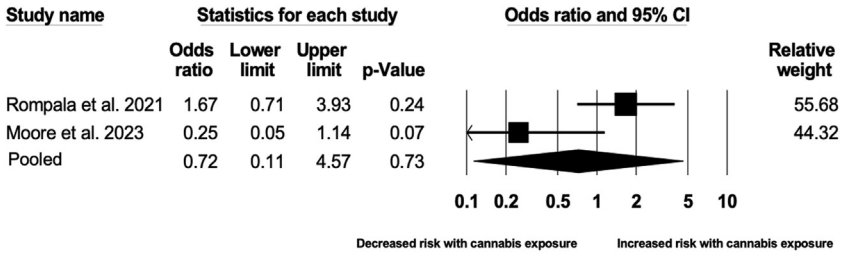
We found a statistically significant association between prenatal cannabis exposure and a 20% increased risk for regular cannabis use in young adulthood, which is mainly derived from the positive association found in the study of Sonon et al,[38] while Porath et al[35] did not report such an association. Differences in cohort characteristics may explain the findings between the 2 studies. Porath et al[35] reported outcomes from the Ottawa Prenatal Prospective Study, a cohort of white, middle-class, and relatively low-risk pregnancy population, which overlooks the numerous stressors typically associated with an environment where cannabis use is present. However, Sonon et al[38] reported outcomes from the MHPCD Study, a cohort of mixed-race, predominantly single, low socioeconomic status, and high-risk pregnancy populations exposed to various environmental stressors alongside cannabis usage. It is worth noting that these studies did not control for additional genetic or environmental factors, such as family history of substance use or poor parenting, which may affect the association found in our analysis.[59,60]

After adjusting for confounders, we were unable to show a significant association with an increased risk for ASD. However, we discovered significantly high heterogeneity in the ASD pooled analysis (I^2=65%), mainly explained by the study of Corsi et al,[33] the only study that reported a statistically significant high risk for ASD. This substantial difference might be derived from this study's large sample size, sufficient to detect statistically significant associations that may have been overlooked in smaller-scale investigations.

One of the major safety concerns regarding the use of cannabis is its association with psychosis and schizophrenia.[61–64] Longitudinal studies reported a dose-response association between cannabis exposure and the risk for psychosis in adults.[65] Therefore, we were interested in exploring whether this association can also be established following prenatal cannabis exposure. We found an approximately 30% nonstatistically significant increased risk for psychotic symptoms, such as visual and auditory hallucinations and delusions. It can be thought that genetic and familial susceptibilities play a role in explaining this association. However, all studies except for Day et al[37] accounted for maternal or first-degree familial history of psychopathology. The analysis of psychotic symptoms exhibits notable heterogeneity (I^2=56%), primarily driven by the study by Paul et al,[40] the only study indicating a statistically significant association. The observed heterogeneity likely stems from variations in outcome measurement methods among the studies, detailed in Table 2. While the lack of statistical significance may appear inconclusive, an upward trend for psychotic symptoms raises important questions and highlights the need for continued research. Except for a single study,[37] the analyzed studies assessed psychotic symptoms in the age range of 10 to 12. Psychosis is typically a symptom of schizophrenia, a disorder that rarely occurs before the age of 15.[66] Therefore, it is still possible that evaluating psychotic symptoms at an older age could uncover additional cases, potentially leading to an increase in the observed effect size.

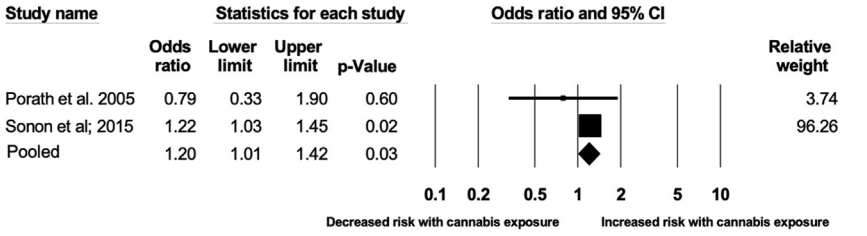
We also observed an association with an approximately 34% increase in the risk for anxiety in the offspring, which did not reach statistical significance, with low to intermediate heterogeneity (I^2=32%). We did not, however, find any association between prenatal cannabis exposure and the risk for depression in the offspring. Only 2 studies examining depression were included in the analysis, presenting conflicting effect size

FIGURE 6
Prenatal cannabis exposure and the risk for depression in the offspring



Odds ratios (OR) and 95% confidence intervals (CI) of random-effects meta-analysis of 2 studies assessing the risk for depression following prenatal cannabis exposure. Test for heterogeneity: χ^2: 4.529, *P*-value=.033; I^2=78%.

FIGURE 7
Prenatal cannabis exposure and the risk for regular cannabis use in the offspring



Odds ratios (OR) and 95% confidence intervals (CI) of random-effects meta-analysis of 2 studies assessing the risk for regular cannabis use in the offspring following prenatal cannabis exposure. Test for heterogeneity: χ^2: 0.91, *P*-value=.34; I^2=0%.

estimates (Figure 6), with high heterogeneity (I^2=78%) probably related to differences in clinical scales used. Furthermore, anxiety and depressive disorders are frequently comorbid[67] and are classified as internalizing disorders.[68] We excluded studies assessing the risk for internalizing disorders or mixed presentation of anxiety and depression, probably limiting our ability to identify robust associations between prenatal cannabis exposure and these specific disorders.

Comparison with existing literature

Prior systematic reviews primarily examined the effects of prenatal cannabis use on subtle cognitive, behavioral, and psychological abnormalities in children.[17–19,69,70] Yet, they did not extensively explore the association between prenatal cannabis exposure and psychiatric or neurodevelopmental abnormalities during childhood. While 1 systematic review noted a trend towards higher attention scores in school-aged children not exposed to cannabis compared to those prenatally exposed, it did not specifically explore the association between prenatal cannabis exposure and a broader spectrum of ADHD-related symptoms, including ADHD diagnosis.[70] The current study distinguishes itself through its quantitative synthesis and updated systematic search, focusing on long-term aspects not thoroughly explored in previous reviews.

Strengths and limitations

Our study has several strengths. We conducted an extensive, up-to-date search of all available databases and included studies missing from previous systematic reviews. We performed a random-effects meta-analysis to pool the results, a method that accounts for heterogeneity. Additionally, we were also able to test for a wide variety of neuropsychiatric conditions. All the studies included in our analysis had an intermediate or low risk of bias, reflected by an NOS score of 6 or above. We included studies with long-term offspring follow-up, enabling us to assess pathologies that develop at different stages of life. Finally, we conducted our analyses using fully adjusted effect size estimates, which allowed us to minimize the influence of various confounding variables.

Our study also has some limitations. First, our meta-analysis is based on data from observational studies, which are highly heterogeneous and might be susceptible to residual confounding and bias that have not been examined in the studies, such as cannabis use after birth and while breastfeeding, the nature of parenting, extrafamilial factors, and other psychosocial influences. Additionally, we cannot rule out that the results of the studies were influenced by confounding by indication. It is possible that maternal psychiatric morbidity, which increases cannabis use, leads to the increased associations observed for some of the neuropsychiatric outcomes. Second, most studies assessed prenatal cannabis consumption by maternal self-report, which cannot exclude recall bias or underreporting of substance use during pregnancy. This may result in exposure misclassification and significant underestimation of the effects of prenatal cannabis exposure.

Furthermore, due to scarce data on the topic, only a limited number of studies were available to analyze each outcome. As a result, we could not conduct a subgroup analysis for outcomes according to the trimester of exposure and the amount of cannabis used, which also prevented our ability to seek a dose-response association. Also, we were unable to assess the potential for publication bias due to the limited number of studies, as each of our outcome analyses included fewer than 10 studies. Finally, it is important to note that most of the studies included in our analysis were conducted on cohorts of women who were pregnant between the 1980s and early 2000s. Cannabis used at those times was characterized by considerably lower Δ9-THC content than currently used compounds.[71,72] Thus, findings presented in the current study may potentially underestimate the impact of contemporary prenatal cannabis exposure on the long-term neuropsychiatric health of children, thereby diminishing the likelihood of detecting robust associations.

Despite the significant impact of cannabis on the developing brain, the complex and largely uncharted etiology of psychiatric morbidity suggests that the clinical influence of prenatal cannabis exposure on psychiatric morbidity may be relatively minor, not necessarily culminating in definitive psychiatric diagnoses or symptoms. While it is plausible that our hypothesis is indeed unfounded, the findings also carry the potential for misinterpretation, given the limitations mentioned above.

Conclusions and implications

Our findings suggest that prenatal cannabis exposure is not associated with a significantly increased risk for ASD, psychotic symptoms, anxiety, and depression in the offspring but may result in a mildly increased risk for ADHD and raise the offspring's vulnerability to cannabis consumption. Still, these results do not confirm the safety of cannabis consumption during pregnancy and should be interpreted with great caution. Our findings warrant further investigation, primarily due to the continuous increase in cannabis potency observed over the last few decades. ■

GLOSSARY

Δ9-THC Δ9-tetrahydrocannabinol
ADHD Attention-deficit/ hyperactivity disorder
ASD Autism spectrum disorder
BASC Behavior Assessment System for Children, Second Edition
CBCL Child Behavior Checklist
CI Confidence interval
MHPCD Maternal Health Practices and Child Development
NOS Newcastle-Ottawa Scale
OR Odds ratio
PAPA The Preschool Age Psychiatric Assessment
PI Prediction interval
RR Risk ratio

REFERENCES

1. Hasin D, Walsh C. Trends over time in adult cannabis use: a review of recent findings. Curr Opin Psychol 2021;38:80–5.
2. American College of Obstetricians and Gynecologists. Marijuana use during pregnancy and lactation. Comm Opin 2017;130:e205–9.
3. Ryan SA, Ammerman SD, O'Connor ME, et al. Marijuana use during pregnancy and breastfeeding: Implications for neonatal and childhood outcomes. Pediatrics 2018;142: e20181889.
4. Meinhofer A, Witman A, Murphy SM, Bao Y. Medical marijuana laws are associated with increases in substance use treatment admissions by pregnant women HHS public access. Addiction 2019;114:1593–601.
5. Wilson S, Rhee SH. Causal effects of cannabis legalization on parents, parenting, and children: a systematic review HHS public access. Prev Med 2022;156:106956.
6. Volkow ND, Han B, Compton WM, McCance-Katz EF. Self-reported medical and nonmedical cannabis use among pregnant women in the United States. JAMA 2019;322: 167–9.
7. World Drug Report 2021 (United Nations publication, Sales No. E.21.XI.8).
8. Skelton KR, Hecht AA, Benjamin-Neelon SE. Association of recreational cannabis legalization with maternal cannabis use in the preconception, prenatal, and postpartum periods. JAMA Netw Open 2021;4:e210138.
9. Taylor DL, Bell JF, Adams SL, Drake C. Factors associated with cannabis use during the reproductive cycle: a retrospective cross-sectional study of women in states with recreational and medical cannabis legalization. Matern Child Health J 2021;25:1491–500.
10. Chang JC, Tarr JA, Holland CL, et al. Beliefs and attitudes regarding prenatal marijuana use: perspectives of pregnant women who report use. Drug Alcohol Depend 2019;196:14.
11. Ko JY, Coy KC, Haight SC, et al. Characteristics of marijuana use during pregnancy — eight states, pregnancy risk assessment monitoring system, 2017. Morb Mortal Wkly Rep 2020;69:1058.
12. Grant KS, Petroff R, Isoherranen N, Stella N, Burbacher TM. Cannabis use during pregnancy: pharmacokinetics and effects on child development. Pharmacol Ther 2018;182:133–51.
13. Jutras-Aswad D, DiNieri JA, Harkany T, Hurd YL. Neurobiological consequences of maternal cannabis on human fetal development and its neuropsychiatric outcome. Eur Arch Psychiatry Clin Neurosci 2009;259:395–412.
14. Smith A, Kaufman F, Sandy MS, Cardenas A. Cannabis exposure during critical windows of development: epigenetic and molecular pathways implicated in neuropsychiatric disease. Curr Environ Health Rep 2020;7:325.
15. Wang X, Dow-Edwards D, Anderson V, Minkoff H, Hurd YL. In utero marijuana exposure associated with abnormal amygdala dopamine D 2 gene expression in the human fetus. Biol Psychiatry 2004;56:909–15.
16. Trezza V, Campolongo P, Manduca A, et al. Altering endocannabinoid neurotransmission at critical developmental ages: impact on rodent emotionality and cognitive performance. Front Behav Neurosci 2012;6:2.
17. Roncero C, Valriberas-Herrero I, Mezzatesta-Gava M, Villegas JL, Aguilar L, Grau-López L. Cannabis use during pregnancy and its relationship with fetal developmental outcomes and psychiatric disorders. A systematic review. Reprod Health 2020;17:1–9.
18. Sharapova SR, Phillips E, Sirocco K, Kaminski JW, Leeb RT, Rolle I. Effects of prenatal marijuana exposure on neuropsychological outcomes in children aged 1-11 years: a systematic review. Paediatr Perinat Epidemiol 2018;32: 512–32.
19. Torres CA, Medina-Kirchner C, O'Malley KY, Hart CL. Totality of the evidence suggests prenatal cannabis exposure does not lead to cognitive impairments: a systematic and critical review. Front Psychol 2020;11:1–28.
20. Sujan AC, Young-Wolff KC, Avalos LA. In-utero cannabis exposure and long-term psychiatric and neurodevelopmental outcomes: the limitations of existing literature and recommendations for future research HHS Public Access. Birth Defects Res 2022;114:689–713.
21. Wells G, Shea BL, O'Connell D, et al. Newcastle-Ottawa scale (NOS) for assessing the quality of nonrandomized studies in meta-analyses 2011. Available at: https://www.ohri.ca/programs/clinical_epidemiology/oxford.asp. Accessed April 18, 2023.
22. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. Eur J Epidemiol 2010;25:603–5.
23. Riley RD, Higgins JPT, Deeks JJ. Interpretation of random effects meta-analyses. BMJ 2011;342:964–7.
24. Borenstein M, Hedges LV, Higgins JPT, Rothstein HR. A basic introduction to fixed-effect and random-effects models for meta-analysis. Res Synth Methods 2010;1:97–111.
25. Szumilas M, Explaining odds ratios. J Can Acad Child Adolesc Psychiatry. 2010;19:227-9.
26. Cummings P. The relative merits of risk ratios and odds ratios. Arch Pediatr Adolesc Med 2009;163:438–45.
27. Davies HTO, Crombie IK, Tavakoli M. When can odds ratios mislead? BMJ 1998;316:989.
28. Zhang J, Yu KF. What's the relative risk?: a method of correcting the odds ratio in cohort studies of common outcomes. JAMA 1998;280: 1690–1.
29. Higgins JPT, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med 2002;21:1539–58.
30. Huedo-Medina TB, Sánchez-Meca J, Marín-Martínez F, Botella J. Assessing heterogeneity in meta-analysis: Q statistic or I2 index? Psychol Methods 2006;11:193–206.
31. Spineli LM, Pandis Hannover N. Prediction interval in random-effects meta-analysis statistics and research design. Am J Orthod Dentofacial Orthop 2020;157:586–94.
32. Gray KA, Day NL, Leech S, Richardson GA. Prenatal marijuana exposure: effect on child depressive symptoms at ten years of age. Neurotoxicol Teratol 2005;27:439–48.
33. Corsi DJ, Donelle J, Sucha E, et al. Maternal cannabis use in pregnancy and child neurodevelopmental outcomes. Nat Med 2020;26: 1536–40.
34. O'connell CM, Fried PA. Prenatal exposure to cannabis: a preliminary report of postnatal consequences in school-age children. Neurotoxicol Teratol 1991;13:631–9.
35. Porath AJ, Fried PA. Effects of prenatal cigarette and marijuana exposure on drug use among offspring. Neurotoxicol Teratol 2005;27:267–77.
36. Zammit S, Thomas K, Thompson A, et al. Maternal tobacco, cannabis and alcohol use during pregnancy and risk of adolescent psychotic symptoms in offspring. Br J Psychiatry 2009;195:294–300.
37. Day NL, Goldschmidt L, Day R, Larkby C, Richardson GA. Prenatal marijuana exposure, age of marijuana initiation, and the development of psychotic symptoms in young adults. Psychol Med 2015;45:1779–87.
38. Sonon KE, Richardson GA, Cornelius JR, Kim KH, Day NL. Prenatal marijuana exposure predicts marijuana use in young adulthood. Neurotoxicol Teratol 2015;47:10–5.
39. Bolhuis K, Kushner SA, Yalniz S, et al. Maternal and paternal cannabis use during pregnancy and the risk of psychotic-like experiences in the offspring. Schizophr Res 2018;202:322–7.
40. Paul SE, Hatoum AS, Fine JD, et al. Associations between prenatal cannabis exposure and childhood outcomes: results from the ABCD study. JAMA Psychiatry 2021;78:64–76.
41. Rompala G, Nomura Y, Hurd YL. Maternal cannabis use is associated with suppression of immune gene networks in placenta and increased anxiety phenotypes in offspring. Proc Natl Acad Sci U S A 2021;118:e2106115118.
42. Murnan AW, Keim SA, Owen K, Boone KM, Sheppard KW, Klebanoff MA. Journal of Applied Developmental Psychology behavioral and cognitive differences in early childhood related to prenatal marijuana exposure. J Appl Dev Psychol 2021;77:101348.
43. DiGuiseppi C, Crume T, Van Dyke J, et al. Peri-pregnancy cannabis use and autism spectrum disorder in the offspring: findings from the study to explore early development. J Autism Dev Disord 2022;52:5064–71.
44. Garrison-desany HM, Hong X, Maher BS, et al. Individual and combined association between prenatal polysubstance exposure and childhood risk of attention-deficit/hyperactivity disorder. JAMA Netw Open 2022;5:e221957.
45. Tchuente V, Sheehy O, Zhao JP, Gorgui J, Gomez YH, Berard A. Is in-utero exposure to cannabis associated with the risk of attention deficit with or without hyperactivity disorder? A cohort study within the Quebec Pregnancy Cohort. BMJ Open 2022;12:1–12.
46. Moore BF, Salmons KA, Hoyt AT, et al. Citation: associations between prenatal and postnatal exposure to cannabis with cognition

and behavior at age 5 years: the healthy start study. Int J Environ Res Public Health 2023;20:4880.
47. Nutor C, Dunlop A, Sadler O, Brennan PA. Prenatal cannabis use and offspring autism-related behaviors: examining maternal stress as a moderator in a Black American cohort. J Autism Dev Disord 2024;54:2355–67.
48. Nomura Y, Ham J, Pehme PM, et al. Association of maternal exposure to Superstorm Sandy and maternal cannabis use with development of psychopathology among offspring: the Stress in Pregnancy Study. BJPsych Open 2023;9:e94.
49. Isik OG, Guo L, Whitehouse AJO, Li G, Ing C. Neurodevelopmental outcomes in children after prenatal marijuana exposure. Paediatr Perinat Epidemiol 2023;37:536–46.
50. Gunn JKL, Rosales CB, Center KE, et al. Prenatal exposure to cannabis and maternal and child health outcomes: a systematic review and meta-analysis. BMJ Open 2016;6:1–8.
51. Luke S, Hutcheon J, Kendall T. Cannabis use in pregnancy in British Columbia and selected birth outcomes. J Obstet Gynaecol Can 2019;41:1311–7.
52. Conner SN, Bedell V, Lipsey K, Macones GA, Cahill AG, Tuuli MG. Maternal marijuana use and adverse neonatal outcomes: a systematic review and meta-analysis. Obstet Gynecol 2016;128:713–36.
53. Marchand G, Masoud AT, Govindan M, et al. Birth outcomes of neonates exposed to marijuana in utero: a systematic review and meta-analysis. JAMA Netw Open 2022;5:e2145653.
54. Baía I, Domingues RMSM. The effects of cannabis use during pregnancy on low birth weight and preterm birth: a systematic review and meta-analysis. Am J Perinatol 2024;41:17–30.
55. Duko B, Dachew BA, Pereira G, Alati R. The effect of prenatal cannabis exposure on offspring preterm birth: a cumulative meta-analysis. Addiction 2023;118:607–19.
56. Marconi A, Di Forti M, Lewis CM, Murray RM, Vassos E. Meta-Analysis of the association between the level of cannabis use and risk of psychosis. Schizophr Bull 2016;42:1262–9.
57. Lowe DJE, Sorkhou M, George TP. Cannabis use in adolescents and anxiety symptoms and disorders: a systematic review and meta-analysis. Am J Drug Alcohol Abuse 2024;50:150–61.
58. Skogli EW, Teicher MH, Andersen PN, Hovik KT, Øie M. ADHD in girls and boys - gender differences in co-existing symptoms and executive function measures. BMC Psychiatry 2013;13:1–12.
59. Agrawal A, Lynskey MT. The genetic epidemiology of cannabis use, abuse and dependence. Addiction 2006;101:801–12.
60. Hayatbakhsh MR, Mamun AA, Najman JM, O'Callaghan MJ, Bor W, Alati R. Early childhood predictors of early substance use and substance use disorders: prospective study 2008;42:720–31.
61. Brañas A, Barrigón ML, Garrido-Torres N, et al. U-shaped curve of psychosis according to cannabis use: new evidence from a snowball sample. J Psychopharmacol 2016;30:1331–8.
62. Alemany S, Arias B, Fatjó-Vilas M, et al. Psychosis-inducing effects of cannabis are related to both childhood abuse and COMT genotypes. Acta Psychiatr Scand 2014;129:54–62.
63. van Gastel WA, Vreeker A, Schubart CD, MacCabe JH, Kahn RS, Boks MPM. Change in cannabis use in the general population: a longitudinal study on the impact on psychotic experiences. Schizophr Res 2014;157:266–70.
64. Di Forti M, Quattrone D, Freeman TP, et al. The contribution of cannabis use to variation in the incidence of psychotic disorder across Europe (EU-GEI): a multicentre case-control study. Lancet Psychiatry 2019;6:427–36.
65. Sami MB, Bhattacharyya S. Are cannabis-using and non-using patients different groups? Towards understanding the neurobiology of cannabis use in psychotic disorders. J Psychopharmacol 2018;32:825–49.
66. Kleinhaus K, Harlap S, Perrin M, et al. Age, sex and first treatment of schizophrenia in a population cohort. J Psychiatr Res 2011;45:136.
67. Axelson DA, Birmaher B. Relation between anxiety and depressive disorders in childhood and adolescence. Depress Anxiety 2001;14:67–78.
68. Kalin NH. The critical relationship between anxiety and depression 2020;177:365–7.
69. Sorkhou M, Singla DR, Castle DJ, George TP. Birth, cognitive and behavioral effects of intrauterine cannabis exposure in infants and children: a systematic review and meta-analysis. Addiction 2024;119:411–37.
70. Thompson M, Vila M, Wang L, Thabane L, Shea AK. Prenatal cannabis use and its impact on offspring neuro-behavioural outcomes: a systematic review. Paediatr Child Health 2023;28:8.
71. Freeman TP, Craft S, Wilson J, et al. Changes in delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD) concentrations in cannabis over time: systematic review and meta-analysis. Addiction 2021;116:1000–10.
72. ElSohly MA, Mehmedic Z, Foster S, Gon C, Chandra S, Church JC. Changes in cannabis potency over the last two decades (1995-2014): analysis of current data in the United States. Biol Psychiatry 2016;79:613–9.

Supplementary Material

APPENDIX A
PRISMA 2020 checklist

Section and topic	Item #	Checklist item	Location where item is reported
Title			
Title	1	Identify the report as a systematic review.	p. 1
Abstract			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	p. 5
Introduction			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	p. 8
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	p. 9
Methods			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	p. 10–11
Information sources	6	Specify all databases, registers, websites, organizations, reference lists, and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	p. 10
Search strategy	7	Present the full search strategies for all databases, registers, and websites, including any filters and limits used.	p. 10
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	p. 11
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	p. 11–12
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (eg, for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	p. 10–11
	10b	List and define all other variables for which data were sought (eg, participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	p. 12
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	p. 12
Effect measures	12	Specify for each outcome the effect measure(s) (eg, risk ratio, mean difference) used in the synthesis or presentation of results.	p. 13

(continued)

APPENDIX A
PRISMA 2020 checklist *(continued)*

Section and topic	Item #	Checklist item	Location where item is reported
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (eg, tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	p. 10—11
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics or data conversions.	p. 13
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	p. 14
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	p. 13—14
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (eg, subgroup analysis, meta-regression).	-
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	14
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	-
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	-
Results			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	p. 15, Figure 1.
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	-
Study characteristics	17	Cite each included study and present its characteristics.	p. 15—18, Tables 1 and 2
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	p. 18—19, Appendix C.
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (eg, confidence/credible interval), ideally using structured tables or plots.	Figures 2—7, Figures D.1—D.4
Results of syntheses	20a	For each synthesis, briefly summarize the characteristics and risk of bias among contributing studies.	p. 18—19, Appendix C.
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (eg, confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	p. 20—22, Figures 2—7, Figures D.1—D.4
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	-
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	p. 20—22
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	-

(continued)

APPENDIX A
PRISMA 2020 checklist *(continued)*

Section and topic	Item #	Checklist item	Location where item is reported
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	-
Discussion			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	p. 24, 27—28, 29—30
	23b	Discuss any limitations of the evidence included in the review.	p. 28—29
	23c	Discuss any limitations of the review processes used.	p. 28—29
	23d	Discuss implications of the results for practice, policy, and future research.	p. 30
Other information			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	p. 10
	24b	Indicate where the review protocol can be accessed or state that a protocol was not prepared.	p. 10
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	-
Support	25	Describe sources of financial or nonfinancial support for the review and the role of the funders or sponsors in the review.	-
Competing interests	26	Declare any competing interests of review authors.	-
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	-

APPENDIX B
MOOSE checklist

Criteria		Brief description of how the criteria were handled in the meta-analysis
Reporting of background should include		
√	Problem definition	The impact of prenatal cannabis exposure on children's neuropsychiatric development is largely inconclusive.
√	Hypothesis statement	Prenatal cannabis exposure increases the risk of neurodevelopmental and psychiatric outcomes in the offspring.
√	Description of study outcomes	Odds ratios (OR) for neuropsychiatric outcomes in the offspring of women exposed to cannabis during pregnancy compared with nonexposed.
√	Type of exposure or intervention used	Prenatal exposure to cannabis or cannabinoid compounds for any medical or recreational use, by any route and at any trimester.
√	Type of study designs used	Observational studies (prospective and retrospective cohort studies, case-control studies).
√	Study population	Offspring whose mothers used cannabis during pregnancy.
Reporting of search strategy should include		
√	Qualifications of searchers	The credentials of the 2 investigators H.B and N.Y.A are indicated in the manuscripts and author contributions.
√	Search strategy, including time period included in the synthesis and keywords	A systematic search was conducted up to January 22, 2024, with no language or date restrictions. The search was performed using various combinations of relevant keywords, as described in "data sources and search strategy" within the methods section.
√	Databases and registries searched	MEDLINE, EMBASE, and Cochrane.
√	Search software used, name and version, including special features	We did not employ software for the search.
√	Use of hand searching	We manually screened the reference lists of selected reviews and eligible studies to ensure that all relevant studies were identified.
√	List of citations located and those excluded, including justifications	Details of the literature search process are outlined in the study flow diagram. The citation list is available upon request.
√	Method of addressing articles published in languages other than English	We placed no restrictions on language in our search strategy.
√	Method of handling abstracts and unpublished studies	We had contacted authors for unpublished studies and missing data, when needed.
√	Description of any contact with authors	In cases of missing relevant information for our analysis, such as effect size estimates with corresponding 95% confidence intervals and number of offspring prenatally exposed to cannabis, the authors of the included studies were contacted to provide us with this additional requested data.
Reporting of methods should include		
√	Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	Detailed inclusion and exclusion criteria are described in the methods section in the manuscript.
√	Rationale for the selection and coding of data	Data extracted from each of the studies were relevant to the exposure (prenatal cannabis consumption), outcome, and possible effect of confounders on the association.
√	Assessment of confounding	We report the adjustments made for potential confounding variables in each study included in the analysis.
√	Assessment of study quality, including blinding of quality assessors; stratification or regression on possible predictors of study results	Study quality was assessed using the Newcastle-Ottawa Scale (NOS). The assessments were carried out independently by the 2 reviewers.

(continued)

APPENDIX B
MOOSE checklist *(continued)*

Criteria		Brief description of how the criteria were handled in the meta-analysis
√	Assessment of heterogeneity	Heterogeneity was measured by Q statistics and I^2 statistics. I^2 reflects the percentage of variation across studies' estimates attributed to the heterogeneity between the studies rather than sampling error.
√	Description of statistical methods in sufficient detail to be replicated	Description of methods of meta-analysis (data synthesis and statistical analysis) are detailed in the methods section in the manuscript.
√	Provision of appropriate tables and graphics	We included the study flow diagram (Figure 1) to describe the search strategy, Table 1 to describe studies' characteristics, Table 2 to describe the measurement methods of outcomes across studies, and forest plots for a graphic summary of all outcomes (Figures 2—7).
Reporting of results should include		
√	Graph summarizing individual study estimates and overall estimate	Figures 2—7
√	Table giving descriptive information for each study included	Table 1
√	Results of sensitivity testing	We conducted sensitivity analyses by excluding studies that deviated significantly from the age ranges of the other studies for each outcome. The results of these sensitivity analyses did not differ substantially from the main analysis, suggesting that variations in offspring age did not significantly impact the overall effect size estimates.
√	Indication of statistical uncertainty of findings	95% confidence intervals and I^2 values were presented with all summary estimates.
Reporting of discussion should include		
√	Quantitative assessment of bias	Publication bias was not assessed.
√	Justification for exclusion	Different outcomes for the same author and cohort were only included once in the analysis.
√	Assessment of quality of included studies	Study quality was assessed using the Newcastle-Ottawa Scale (NOS). Studies' quality ratings are reported in Table 1, with detailed description in Appendix C.
Reporting of conclusions should include		
√	Consideration of alternative explanations for observed results	We discussed potential unmeasured confounders such as genetic and environmental factors. Also, we discussed confounding by indication; maternal psychiatric morbidity, which increases cannabis use, may lead to the increased associations observed for some of the neuropsychiatric outcomes. In addition, maternal self-report on prenatal cannabis use may result in exposure misclassification and significant underestimation of the effects of prenatal cannabis exposure. Finally, older data may not accurately reflect the strength of modern cannabis products, which can make it less likely to find a positive association.
√	Generalization of the conclusions	All studies were conducted among women of childbearing age who probably used cannabis for recreational purposes. Therefore, the conclusion may be generalized to this population only.
√	Guidelines for future research	Our results do not confirm the safety of cannabis consumption during pregnancy and should be interpreted with great caution. Our findings warrant further investigation, primarily due to the continuous increase in cannabis potency observed over the last few decades.
√	Disclosure of funding source	No external funding was used for the review.
√	PROSEPERO registry	CRD42021252601

APPENDIX C

Newcastle-Ottawa Scale (NOS) ratings (stars)[a]

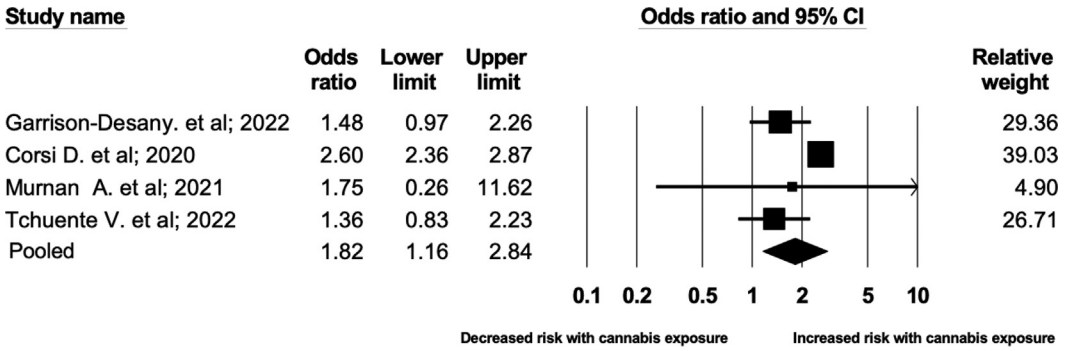
Author, year	Selection	Comparability[b]	Outcome[c]	Total rating
O'connell and Fried[34], 1991	4	2	2	8
Porath and Fried[35], 2005	4	1	3	8
Gray et al[32], 2005	4	1	2	7
Zammit et al[36], 2009	3	2	2	7
Day et al[37], 2015	3	2	2	7
Sonon et al[38], 2015	3	1	2	6
Bolhuis et al[39], 2018	4	2	1	7
Corsi et al[33], 2020	3	2	3	8
Paul et al[40], 2021	3	2	1	6
Rompala et al[41], 2021	3	2	2	7
Murnan et al[42], 2021	4	1	2	7
DiGuiseppi et al[43], 2021	3	2	2	7
Garrison-Desany et al[44], 2022	4	2	1	7
Tchuente et al[45], 2022	3	2	3	8
Moore et al[46], 2023	4	1	1	6
Nutor et al[47], 2023	2	2	2	6
Nomura et al[48], 2023	4	2	2	8
Isik et al[49], 2023	3	2	1	6

[a] A study can be awarded a maximum of 4 stars in Selection category, a maximum of 2 stars in Comparability category, and a maximum of 3 stars in Outcome category; [b] In the Comparability category, a study can receive 1 star if it controls for other substance use during pregnancy and receive another star if the study controls for any other additional factor; [c] In the "adequacy of follow-up of cohorts" item within the Outcome category, a study can be awarded a star if the follow-up rate is above 80%.

Appendix D. Meta-analysis using crude effect size estimates for ADHD, ASD, anxiety, and psychotic symptoms outcomes

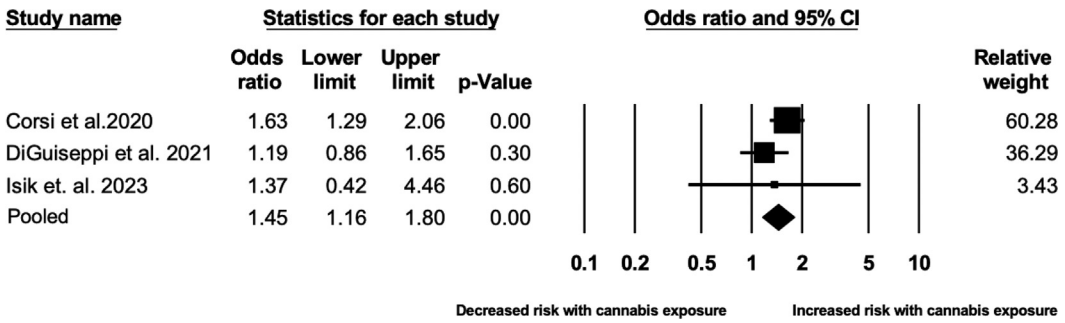
.

FIGURE D.1
Prenatal cannabis exposure and the risk for attention-deficit/hyperactivity disorder (ADHD) in the offspring



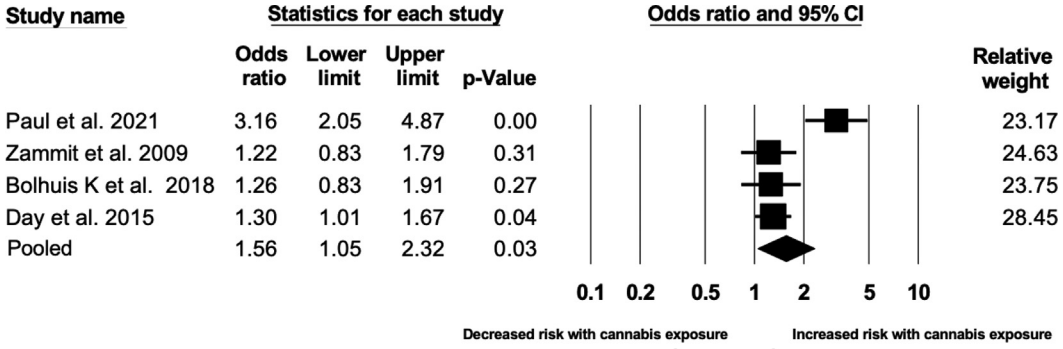
Crude odds ratios (OR) and 95% confidence intervals (CI) of random-effects meta-analysis of 4 studies assessing the risk for attention-deficit/hyperactivity disorder (ADHD) following prenatal cannabis exposure, using unadjusted effect size estimates. Test for heterogeneity: χ^2: 12.356, *P*-value=.006; I^2=75%.

FIGURE D.2
Prenatal cannabis exposure and the risk for autism spectrum disorder (ASD) in the offspring



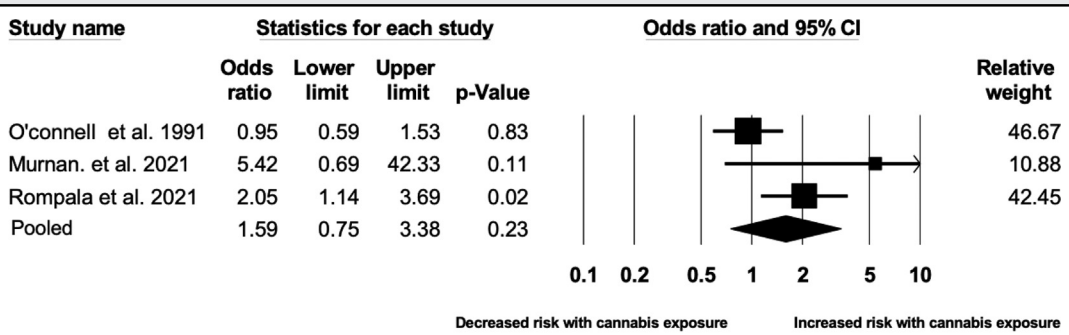
Crude odds ratios (OR) and 95% confidence intervals (CI) of random-effects meta-analysis of 3 studies assessing the risk for autism spectrum disorder (ASD) following prenatal cannabis exposure, using unadjusted effect size estimates. Test for heterogeneity: χ^2: 2.347, *P*-value=.309; I^2=14%.

FIGURE D.3
Prenatal cannabis exposure and the risk for psychotic symptoms in the offspring



Crude odds ratios (OR) and 95% confidence intervals (CI) of random-effects meta-analysis of 4 studies assessing the risk for psychotic symptoms following prenatal cannabis exposure, using unadjusted effect size estimates. Test for heterogeneity: χ^2: 14.340, *P*-value=.002; I^2=79%.

FIGURE D.4
Prenatal cannabis exposure and the risk for anxiety in the offspring



Crude odds ratios (OR) and 95% confidence intervals (CI) of random-effects meta-analysis of 3 studies assessing the risk for anxiety following prenatal cannabis exposure, using unadjusted effect size estimates. Test for heterogeneity: χ^2: 5.804, *P*-value=.055; I^2=65%.