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REVIEW

ADDICTION SSA

The effect of prenatal cannabis exposure on offspring preterm birth: a cumulative meta-analysis

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Abstract

Background and aims: Mixed results have been reported on the association between prenatal cannabis exposure and preterm birth. This study aimed to examine the magnitude and consistency of associations reported between prenatal cannabis exposure and preterm birth.

Methods: This review was guided by the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines. We performed a comprehensive search of the literature on the following electronic databases: PubMed, EMBASE, SCOPUS, Psych-INFO and Web of Science. The revised version of the Newcastle–Ottawa Scale (NOS) was used to appraise the methodological quality of the studies included in this review. Inverse variance weighted random-effects cumulative meta-analysis was undertaken to pool adjusted odds ratios (aOR) after sequential inclusion of each newly published study over time. The OR and 95% confidence interval (CI) limits required (stability threshold) for a new study to move the cumulative odds ratio to the null were also computed.

Results: A total of 27 observational studies published between 1986 and 2022 were included in the final cumulative meta-analysis. The sample size of the studies ranged from 304 to 4.83 million births. Prenatal cannabis exposure was associated with an increased risk of preterm birth (pooled aOR = 1.35, 95% CI = 1.24–1.48). The stability threshold was 0.74 (95% CI limit = 0.81) by the end of 2022.

Conclusions: Offspring exposed to maternal prenatal cannabis use was associated with higher risk of preterm birth, which warrants public health messages to avoid such exposure, particularly during pregnancy.

KEYWORDS
Cannabis, cumulative meta-analysis, offspring, pregnancy, preterm birth, stability thresholds

INTRODUCTION

Preterm birth is often defined as babies born alive prior to 37 completed weeks of gestation [1]. Estimates from the World Health Organization (WHO) in 2018 suggested that the world-wide prevalence of preterm birth is 11% suggesting that, globally, approximately 15 million babies are born preterm every year [1, 2]. Preterm birth and its complications are responsible for 18% of early childhood mortality and more than 35% of all deaths among neonates [3]. Elevated risk of hearing [4, 5], respiratory diseases [6], cardiac dysfunction [7], mental health and behavioural problems [8, 9] and other disabilities [10] have been observed in children and adults born prematurely. Identifying

and understanding potentially modifiable risk factors for preterm birth is therefore critically important to elucidate the pathways that lead to preterm birth and reduce its incidence and associated sequelae.

Preterm birth is believed to be caused by several risk factors and involves multiple mechanisms [11–13]. Some studies have claimed that maternal cannabis use during pregnancy is one such risk factor [14]. Globally, cannabis is one of the most widely cultivated, trafficked and used psychoactive drugs [15]. According to WHO reports, the global annual prevalence of cannabis consumption in 2016 was estimated to be 2.5%, suggesting that approximately 147 million people consume cannabis annually [15]. It is also one of the most common drugs consumed during the prenatal period [16, 17].

Epidemiological studies on the association between prenatal cannabis exposure and preterm birth have reported conflicting results [14, 18, 19]. While a large prospective longitudinal study found a 41% increased risk of preterm birth in mothers who reported prenatal cannabis use [16], other studies have reported null associations [17, 20, 21]. Further, the two existing systematic reviews and meta-analyses conducted to date have also reported conflicting findings [22, 23]. Of these two reviews, one meta-analysis by Gunn *et al.* reported a null association [22]. [22]. However, the Gunn review included only nine studies, did not control for tobacco use and did not conduct subgroup analysis to further explore the potential source of heterogeneity throughout the included studies. The second meta-analysis by Conner *et al.* [23] pooled estimates from more studies and reported an adverse association between prenatal cannabis use and preterm birth [pooled adjusted relative risk (RR) of 1.32, 95% confidence interval (CI) = 1.14–1.54]. However, when analyses in the Conner review were stratified by the studies that adjusted for prenatal tobacco exposure, the association did not remain (RR = 1.08, 95% CI = 0.82–1.43), suggesting that prenatal tobacco smoking is an important confounder. Since the publications of Conner review [23], the number of published epidemiological studies on the topic has almost doubled [14, 16–21, 24–28], suggesting the need and ability to update the evidence. The aim of this study was (i) to conduct a systematic review and meta-analysis including cumulative meta-analysis to examine the magnitude and sufficiency of associations reported between maternal cannabis exposure during pregnancy and preterm birth and (ii) to apply the method to establish stability threshold for pooled estimates to see if the aggregate evidence can be considered stable.

METHODS

Research design

This study was guided by the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines [29]. The protocol of this review was prospectively registered in the International Prospective Register of Systematic Reviews (PROSPERO), with the registration number of CRD42022304816. A pre-registered protocol was followed to guide the literature search strategy, identification of the relevant studies, data extraction and analysis.

Data sources and literature searches

We performed a comprehensive search of literature on the following electronic databases—PubMed, EMBASE, SCOPUS, Psych-INFO and Web of Science—to identify studies that examined the association between prenatal cannabis exposure and preterm birth. Systematic literature searches did not have date and language limits. The search terms and keywords were: '[(cannabis use OR cannabis smoking OR cannabis exposure OR marijuana use OR marijuana smoking OR marijuana exposure) AND (prenatal OR antenatal OR pregnancy OR maternal OR gestational OR perinatal) AND (pregnancy complications OR pregnancy outcomes OR birth outcomes OR preterm birth OR preterm delivery OR prematurity OR premature babies OR neonatal outcomes OR child health outcomes)]' (Supporting information, File S1). The search comprised both Medical Subject Headings (MeSH) and free text words. These keywords were first created in PubMed and then formatted accordingly to the respective databases. Additionally, we also performed manual searches for other potential studies by reviewing the reference lists of identified studies.

Eligibility criteria

Inclusion criteria

We included primary studies in this systematic review and meta-analysis if (i) they were carried out using observational study designs such as case–control, cohort, case–cohort, nested case control and cross-sectional study designs; (ii) reported prenatal cannabis use as an exposure; and preterm birth as an outcome of interest; (iii) measured outcomes using OR, risk ratio or relative risk (RR) estimates or reported data to calculate point estimates; and (iv) reported 95% CIs or data to calculate interval estimates.

Exclusion criteria

Case reports, editorials, letters, commentaries, non-peer-reviewed articles, studies conducted on animals, and conference or meeting abstracts were excluded from the review.

Study outcome

The outcome of interest of this systematic review and meta-analysis was preterm birth. Preterm birth was operationalized as 'birth before 37 weeks of completed gestation'.

Data extraction

Two independent reviewers (B.D. and B.A.D.) performed data extraction using the standardized data extraction form. First author (study

name), year of publication, geographical location of the study (country), study design, sample size, confounders and covariates included in the fully adjusted model, odds ratios (ORs) or RR or risk ratio with their corresponding 95% CIs and time and ascertainment of prenatal cannabis exposure were systematically extracted from the studies included in this review, in accordance with the PRISMA guidelines [29]. Any sources of cannabis use or smoking, either self-report or clinical or laboratory report were included in the review.

Quality appraisal of the included studies

Two independent reviewers (B.D. and B.A.D.) appraised the methodological quality of the studies included in this review using the revised version of the Newcastle–Ottawa Scale (NOS) [30]. This scale uses three standard scoring categories: high quality (scored 7–9), moderate quality (scored 4–6) and low quality (scored 0–3) and has been widely accepted for quality appraisal of case–control and cohort studies. These scorings were based on the three broad perspectives, namely: selection of the study groups (selection of case and control); comparability between the groups (comparability of cases and controls); and ascertainment of outcome (ascertainment of exposure). Additionally, an adapted version of the NOS was specifically used to assess the methodological quality of cross-sectional studies included in this review [31]. The scoring of this adapted version was based on the following three broad perspectives: selection, comparability and outcome. The adapted version of the NOS uses four scoring categories: very good studies (9–10 points), good studies (7–8 points), satisfactory studies (5–6 points) and unsatisfactory studies (0–4 points). Conflicting scores between two reviewers were resolved via discussion.

Data synthesis and analysis

A cumulative meta-analysis was performed using Stata version 16.1. Studies that reported an effect estimate such as OR/RR or have data required to compute these were included in the final cumulative meta-analysis. To determine how the pooled estimate and its precision changes over time, studies were ordered by increasing year of publication and then cumulative meta-analysis was repeatedly undertaken after sequential inclusion of each newly published study over time. A stability threshold was estimated to determine if the aggregate evidence can be considered stable or whether inferences are sensitive to the findings of a new study [32]. If the studies reported multiple estimates, the estimate (OR/RR) with most extensive adjustment were used for a cumulative meta-analysis. If the studies included in the cumulative meta-analysis reported several outcomes such as spontaneous preterm birth, iatrogenic preterm birth or preterm birth classified by extent of prematurity (extremely preterm, very preterm, moderately preterm, late preterm birth), the estimate for all preterm birth was reported in the cumulative meta-analysis. For the studies that reported estimates for individual trimesters of exposure but not for the whole pregnancy period, the estimates for the first trimester prenatal exposure to cannabis were included in the final analysis. Due to substantial heterogeneity throughout studies, inverse variance weighted random-effects cumulative meta-analysis model used to combine studies to estimate the association between prenatal cannabis exposure and preterm birth [33]. Because the prevalence of preterm birth was low (< 10%) in all studies, we assumed that ORs were equivalent to RRs. However, as most studies included in the current cumulative meta-analysis reported risk estimates as adjusted ORs (aORs), we also reported all risk estimates as aORs. Subgroup analyses were also performed to explore the potential source of heterogeneity among studies included in the meta-analysis. The magnitude of statistical heterogeneity among studies was detected by the Cochrane's Q- and I^2-tests [34]. We also conducted an additional sensitivity analysis using unadjusted RR/OR. Potential publication bias was assessed by inspection of the funnel plot and Egger's test for regression asymmetry [35].

RESULTS

Study selection

Our initial systematic literature search yielded a total of 6676, of which 6621 records were excluded after title and abstract review, as they were not related to the topic of interest. A total of 55 articles were retained for full-text review and, of these, 27 articles (16 new articles and 11 original studies from the previous systematic reviews and meta-analyses) were included in the current meta-analysis (Fig. 1).

Characteristics of studies included in the systematic review and meta-analysis

Studies included in the current meta-analysis were published between 1986 and 2022 [21, 36]. These observational studies were conducted in four developed countries: 16 studies were conducted in the United States [14, 20, 21, 24, 25, 27, 28, 36–44], four in Australia [17, 45–47], one was based in Australia and recruited pregnant women from Australia, New Zealand, Ireland and the United Kingdom [19], four in Canada [16, 18, 26, 48] and two in France [49, 50]. Of the included studies, 22 were cohort and five studies were cross-sectional. The sample size of the studies included in this systematic review and meta-analysis ranged from 304 to 4.83 million study participants. Seventeen studies recruited study participants from community settings (population-based), whereas 10 studies were from clinical settings (Table 1).

Confounding variables in multivariable models

Statistical adjustment for potential confounders and covariates varied throughout studies included in this review. Maternal age and educational attainment were included as adjustment variables in

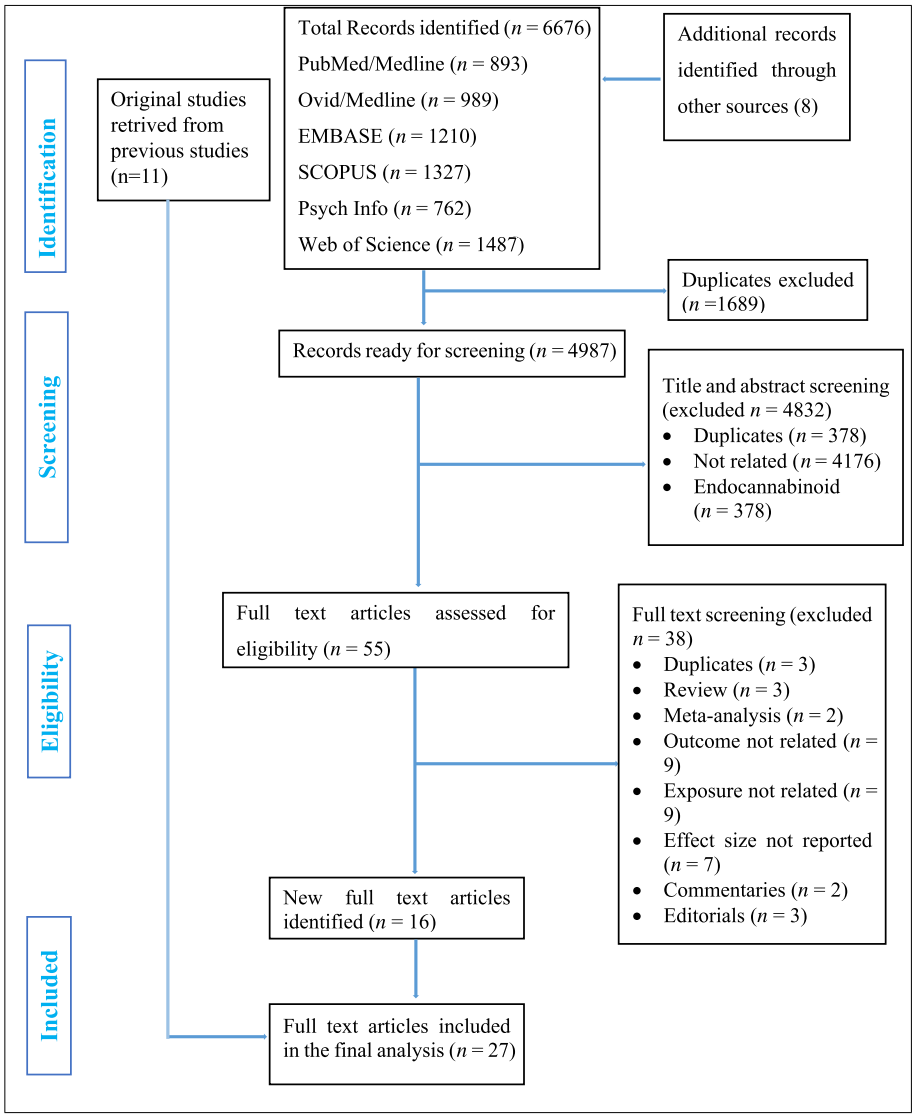

FIGURE 1 Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) flow-chart of review search

almost all studies (Table 1). Eight studies adjusted for family or household income. Most studies adjusted for maternal tobacco smoking during pregnancy, whereas 16 studies adjusted for maternal prenatal alcohol consumption and other drugs. Twelve studies adjusted for pre/gestational diabetes and/or per/gestational hypertensive disorders of pregnancy (mainly pre-eclampsia) (Supporting information, File S2).

Prenatal cannabis exposure and outcome

All studies used a categorical measure to ascertain prenatal cannabis exposure. Eighteen studies used self-reports of cannabis use during pregnancy. Six studies used the International Classification of Diseases and related health problems (ICD-9 and -10) to assess prenatal cannabis exposure. Four studies used urine toxicology tests (Table 1). All studies included in this review defined preterm birth as 'birth before 37 weeks of completed gestation'.

Quality appraisal of included studies

Based on the revised NOS, all studies included in this meta-analysis were classified as good in quality. Of the 22 cohort studies included in the analysis, five scored 9, 12 scored 8 and five scored 7. Based on the modified version of NOS, one cross-sectional study scored 7, three studies scored 8 and one study scored 9 (Supporting information, File S3).

Prenatal cannabis exposure and risk of preterm birth

Maternal prenatal cannabis exposure was associated with an increased risk of preterm birth with a pooled aOR of 1.35, 95% CI = 1.24–1.48 (Supporting information, File S4). Results from the cumulative meta-analysis of ORs also yielded similar estimates (Fig. 2). Observed estimates regarding sufficiency were robust to the type of meta-analysis conducted. When cumulative meta-analyses repeated

TABLE 1 Summary of studies included in the current meta-analysis

Study name	Country	Study design	Sample size	Prenatal cannabis exposure	aOR (95% CI)	Adjusted for
Bada 2005	USA	Cohort	8637	Assessed by self-report	0.90 (0.73–1.11)	Maternal medical and obstetric complications, any hospitalization during pregnancy, maternal weight gain during pregnancy, PNC, maternal age, Medicaid insurance and infant's gender, and race, clinical site and legal and illegal drug use (tobacco, alcohol, cocaine and opiates)
Crume 2018	USA	Cross-sectional study	3207	Assessed by self-report	1.30 (0.8–2.1)	Maternal age, ethnicity, level of education, prenatal tobacco use
Nguyen 2022	USA	Cohort	30 727	Assessed by self-report and urine test	1.16 (0.92–1.45)	Maternal age, marital status, parity, maternal race/ethnicity, maternal education, prenatal care, health insurance, cigarette smoking during pregnancy, state/territory of residence and year of interview
Bandoli 2021	USA	Cohort	29 112	Measured by ICD-10	1.40 (1.3–1.6)	Pregnancy BMI, race and ethnicity, payer source, anxiety, depression, bipolar disorder, pre-existing hypertension, pre-existing diabetes, maternal age and education and alcohol use, nicotine use and other substance-related diagnoses
Warshak 2015	USA	Cohort	6468	Assessed by self-report	1.04 (0.91–1.19)	Maternal age, race, parity, BMI class and no prenatal care, induction, CS delivery after labour, gestational diabetes, pre-eclampsia
Brown 2016	Australia	Cross- sectional study	344	Assessed by self-report	2.30 (0.6–8.3)	Educational level, employment history, maternal age, no. of children, stressful events and social health issues, diabetes and hypertension during pregnancy, tobacco use in pregnancy
Bonello 2014	Australia	Cohort	304	Assessed by ICD-10-AM-F10.	3.26 (1.52–6.97)	Maternal age, maternal country of birth, smoking status, remoteness of living area, and the Index of Relative Socio-economic Disadvantage, pre-existing maternal diabetes and hypertension, pre-eclampsia, gestational diabetes, method of birth, infant gender and fetal/neonatal death
Corsi 2019	Canada	Cohort	661 617	Assessed by self-report	1.41 (1.36–1.47)	Maternal age, parity, area-level income quintile, smoking status, alcohol use, opioid use, selective serotonin reuptake inhibitor use, other drug use, maternal mental health conditions, antenatal care and year of birth, pre-eclampsia, gestational diabetes
Hayatbakhsh 2011	Australia	Cohort	24 874	Assessed by self-report	1.50 (1.1–1.9)	Maternal age, parity, ethnicity, weight, prenatal alcohol and tobacco use, another drug use
Kharbanda 2020	USA	Cohort	3435	Assessed by self-report and urine toxicology test at first antenatal visit	1.06 (0.64–1.77)	Maternal age, ethnicity, insurance, pre-pregnancy BMI, use of folic acid, other drug use, smoking during pregnancy,

(Continues)

TABLE 1 (Continued)

Study name	Country	Study design	Sample size	Prenatal cannabis exposure	aOR (95% CI)	Adjusted for
						hypertension, diabetes, sickle cell disease, lupus and other rheumatological disorder, seizure
Cubizolles 2013	France	Cross- sectional study	13 545	Assessed by self-report	2.15 (1.1–4.18)	Mother's age, parity, nationality, cohabiting, level of education, employment status, income of the household, BMI and alcohol consumption
Van Gelder 2010	USA	Cohort	5871	Assessed by structured interview	1.00 (0.60–1.90)	Cigarette smoking, binge drinking, and gestational weight gain.
Shiono 1995	USA	Cohort	7470	Assessed by self-report	1.10 (0.80–1.30)	Maternal age, education, ethnicity, income, employment, living arrangement, prenatal tobacco and alcohol exposures, BMI
Hatch 1986	USA	Cohort	3857	Assessed by self-report	1.90 (1.00–3.90)	Maternal age, race, parity, education, marital status, history of stillbirth, spontaneous abortion, or induced abortion, cigarette smoking, and average daily alcohol and caffeine intake
Kliegman 1994	USA	Cohort	425	Assessed by self-report and biological samples	1.89 (0.34–10.5)	Race, age < 19 years, history of alcohol use during the pregnancy, history of cocaine use, cigarette use, history of prior sexually transmitted diseases (syphilis, gonorrhoea, chlamydia infection, pelvic inflammatory disease), having had more than three children previously, no prenatal care and a history of a prior preterm birth.
Shi 2021	USA	Cohort	4.83 million	Measured by ICD-9, clinical modification	1.06 (1.01–1.12)	Mothers' age, educational attainment, ethnicity, health insurance, delivery mode and birth history, mothers' hypertension, diabetes, thyroid disease, anaemia, cardiovascular disease, and pain, major depressive disorder, anxiety disorder and other mental disorders, adequate prenatal care, tobacco use, alcohol use disorder, opioid use disorder and other drug use disorders
Michalski 2020	Canada	Cohort	2229	Assessed by self-report	1.26 (0.62–2.57)	Age, year of LSQ completion, pre-pregnancy BMI, household income, education, ethnicity, alcohol use, tobacco use, anxiety or depression symptoms, prescription anti-depressant use, and prescription pain medication use
Leemaqz 2016	Australia	Cohort	5588	Assessed by self-report	2.28 (1.45–3.59)	Maternal age, BMI, SE index, medical and family history, cigarette smoking
Wong 2019	Canada	Cohort (medical charts)	25 263	Assessed by self-report	1.71 (0.70–4.15)	Maternal age, BMI, previous preterm birth, depression and anxiety during pregnancy, tobacco and alcohol use, neighbourhood
Baer 2019	USA	Cohort (medical charts)	2.89 million	Assessed by self-report	1.20 (1.10–1.40)	Race, age at delivery, payment for delivery, maternal education, pre-pregnancy BMI, adequacy of prenatal care,

(Continues)

TABLE 1 (Continued)

Study name	Country	Study design	Sample size	Prenatal cannabis exposure	aOR (95% CI)	Adjusted for
						any diabetes, hypertension, alcohol and tobacco use, mental illness, and preterm birth
Haight 2021	USA	Cross-sectional study	5548	Assessed by self-report	1.10 (0.60–2.00)	Maternal age, race, marital status, education, pre-pregnancy BMI, insurance, parity, timing of prenatal care, tobacco smoking
Prunet 2017	France	Cross- sectional study	14 326	Assessed by self-report	1.90 (1.10–3.30)	Parity, previous preterm birth and induced abortion, planned pregnancy, fertility treatment, pre-pregnancy BMI, educational level, employment, inadequate prenatal care
Nawa 2020	USA	Cohort	8261	Assessed by self-report	1.15 (0.95–1.40)	Maternal age, BMI, race, marital status, parity, education, income, alcohol and tobacco use during pregnancy, child sex, year of child's birth
Chabarria 2016	USA	Cohort	12 069	Assessed by self-report	0.84 (0.35–3.87)	Maternal age, parity, race, marital status, mode of delivery, gestational and pregestational diabetes and hypertension
Luke 2019	Canada	Cohort	243 140	Assessed by self-report	1.27 (1.14–1.42)	Maternal age, pre-pregnancy BMI, tobacco use, alcohol use, other substance use, socio-economic status, race
Oni 2022	Australia	Cohort	622 640	Measured by ICD-10-AM	2.60 (2.20–3.00)	Maternal age, tobacco smoking, indigenous status, health insurance, antenatal care attendance, plurality of birth, pre-eclampsia, gestational hypertension, chronic/pre-existing hypertension, pre-existing and gestational diabetes, history of substance use disorders (opioids, alcohol, hypnotics, hallucinogens, volatile solvents,
Petrangelo 2018	USA	Cohort	1.25 million	Measured by ICD-9	1.40 (1.36–1.43)	Age, race, hospital location or teaching, income, insurance, multiple pregnancy, pre-existing diabetes, hypertension, smoking, alcohol, and another illicit drug use

aOR = adjusted odds ratio; CI = confidence interval; PNC = postnatal care; BMI = body mass index; CS = caesarean section; LSQ = lifestyle questionnaires; SE index = Socioeconomic index.

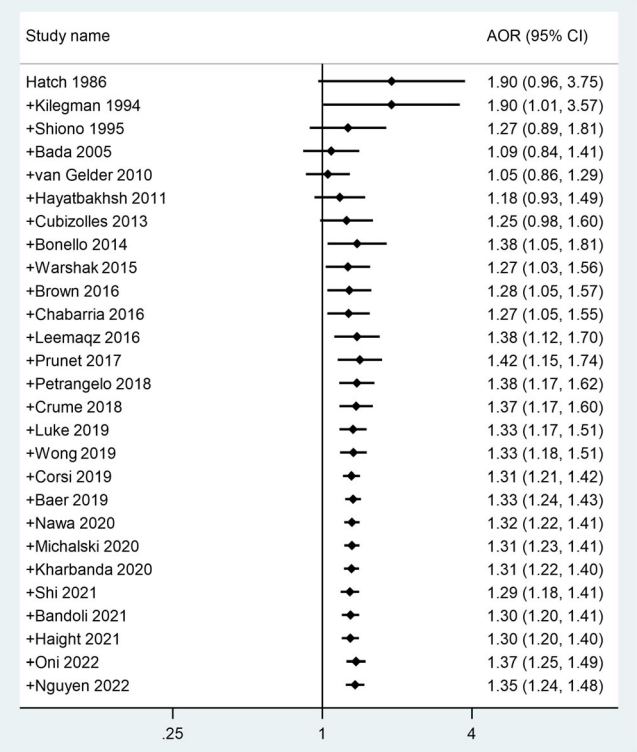

FIGURE 2 Converging cumulative odds ratio (COR) with each successive publication on the association between prenatal cannabis exposure and preterm birth (based on random-effects estimator). The '+' symbol indicates sequential addition of the study results to those previously published. AOR = Adjusted Odds Ratio.

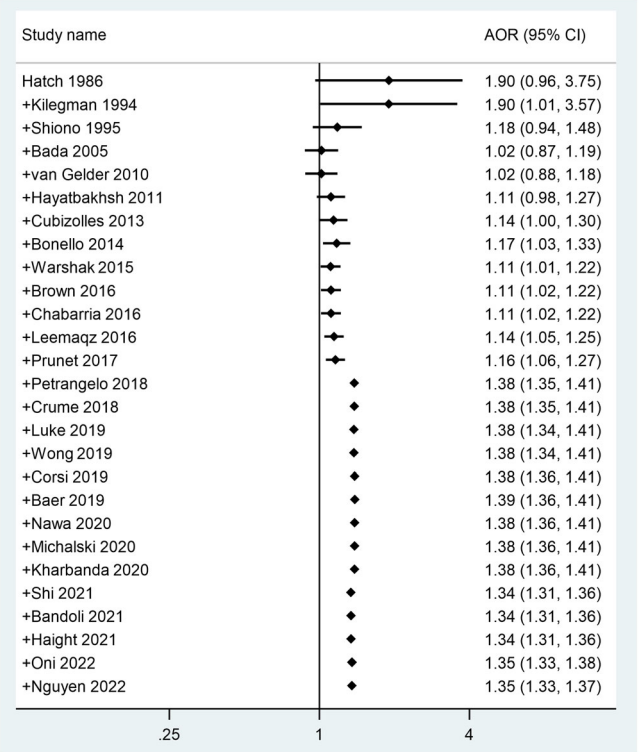

FIGURE 3 Converging cumulative odds ratio (COR) with each successive publication on the association between prenatal cannabis exposure and preterm birth (based on fixed-effects estimator). The '+' symbol indicates sequential addition of the study results to those previously published. AOR = Adjusted Odds Ratio.

with a fixed-effects model, we observed similar results to that of random-effect estimators (Fig. 3), indicating the robustness of our finding irrespective of the type of meta-analysis undertaken. The final stability threshold was 0.74 (95% CI limit = 0.81), meaning that to change the conclusion of this study, a new observational study would need to report a protective aOR of 0.74 (95% CI limit = 0.81), with precision similar to that observed by the past 27 epidemiological studies combined. Observed estimates reported by studies published after 2014 resulted in negligible change to the point estimates (OR) and marginal improvements in precision but no change in the direction of association. We observed substantial heterogeneity throughout studies included in the meta-analysis (I^2 = 88.4%; Q = 224.12; *P*-value < 0.001). Egger's regression test [*B* = 0.04, standard error (SE) = 0.71, *P*-value = 0.96] and visual inspection of the funnel plot (symmetric) revealed insufficient evidence to suggest the influence of publication bias (Fig. 4).

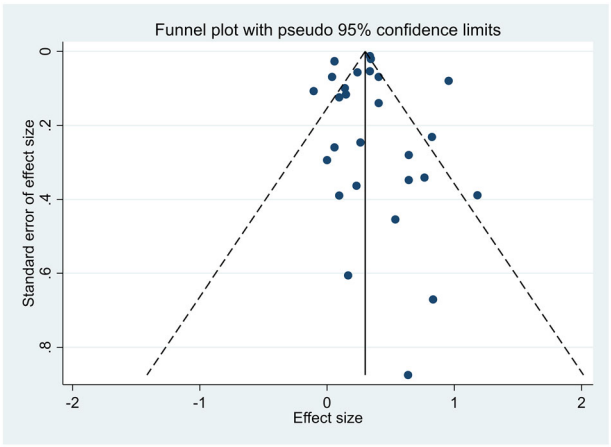

FIGURE 4 Funnel plot showing no evidence of publication bias

Subgroup and sensitivity analysis

Adjustment for maternal tobacco, alcohol and exposure to other drugs during pregnancy, gestational diabetes, hypertension, household income and previous preterm birth did not change the association between prenatal cannabis exposure and preterm birth (Table 2). Similarly, the association observed in this study was not substantially influenced by variation in the study design, sample size, the study's geographical location and the source in which the study participants were recruited. The risk of preterm birth in offspring exposed to maternal prenatal cannabis use was substantially elevated in the studies that used a cross-sectional study design (aOR = 1.59, 95% CI = 1.19–2.12) compared to cohort design (aOR = 1.34, 95% CI = 1.22–1.46). The risk of preterm birth in offspring exposed to

prenatal cannabis use was considerably more elevated in the studies that did not adjust for prenatal tobacco exposure (aOR = 1.70, 95% CI = 1.03–2.79) compared to those where adjustment was made (aOR = 1.35, 95% CI = 1.23–1.47). Similarly, the risk of preterm birth was slightly greater in the studies that did not control for maternal alcohol and/or other drug use during pregnancy (aOR = 1.58, 95% CI = 1.14–2.19) when compared to those adjusted for such exposure (aOR = 1.28, 95% CI = 1.18–1.40). The risk of preterm birth in offspring exposed to prenatal cannabis use was somewhat similar in the studies that did not adjust for pre-pregnancy/gestational hypertension or diabetes (aOR = 1.36, 95% CI = 1.21–1.53) when compared to the studies that included such risk factors in their final models (aOR = 1.31, 95% CI = 1.18–1.45). We also conducted a sensitivity analysis based on the level of adjustment for previous preterm birth, and observed an increased risk of preterm birth in the studies that did not include this risk factor in their final model (aOR = 1.52, 95% CI = 1.34–1.72) when compared to those studies that included this risk factor (aOR = 1.33, 95% CI = 1.21–1.46). To further explore the source of heterogeneity throughout studies included in this review, we conducted a sensitivity analysis after restriction to the studies that included household income in their final model. The OR of preterm birth in the studies that did not adjust for household income (aOR = 1.38, 95% CI = 1.17–1.63) was not higher when compared to those studies that included this risk factor in their models (aOR = 1.35, 95% CI = 1.28–1.44) (Table 2).

The OR of preterm birth was higher in the studies that recruited the study participants' clinical or hospital setting (aOR = 1.56, 95% CI = 1.25–1.95) when compared to the study participants recruited from population-based registers (aOR = 1.27, 95% CI = 1.14–1.42). The direction of effect was consistently positive, and the magnitude of the effect varied by study location. We found that the OR of preterm birth was more elevated in the studies that originated from Australia (aOR = 2.20, 95% CI = 1.60–3.03) and France (aOR = 2.00, 95% CI = 1.31–3.05) than the United States and Canada (Table 2). Moreover, we did not observe substantial variation in the estimates when repeating a sensitivity analysis restricting to the studies that reported crude or unadjusted OR/RR (Supporting information, File S5).

DISCUSSION

This meta-analysis investigated the risk of preterm birth in offspring exposed to prenatal cannabis use reported in 27 observational studies. We found consistent evidence of an association between prenatal cannabis exposure and preterm birth. It was demonstrated that the cumulative evidence for the existence of an adverse association

TABLE 2 Subgroup analysis of studies included in the meta-analysis

Subgroups		No. of studies	Pooled adjusted odds ratios (aOR)	95% CI	Heterogeneity within the studies	
					I^2 (%)	*P*-value
Study design	Cohort	22	1.34	1.22–1.46	90.4	< 0.001
	Cross-sectional	5	1.59	1.19–2.12	–	0.548
Setting study participants were recruited	Hospital or clinical	9	1.27	1.14–1.42	85.2	< 0.001
	Population-based register	18	1.56	1.25–1.95	88.7	< 0.001
Sample size based on median	≤ 8637	14	1.22	1.04–1.42	51.7	0.013
	> 8637	13	1.45	1.30–1.60	88.4	< 0.001
Geographical location study was originated	USA	16	1.19	1.07–1.33	88.3	< 0.001
	Australia	5	2.20	1.60–3.03	68.3	0.013
	Canada	4	1.38	1.30–1.46	11.1	0.337
	France	2	2.00	1.31–3.05	–	0.779
Studies adjusted for prenatal tobacco exposure	Yes	22	1.35	1.23–1.47	89.5	< 0.001
	No	5	1.70	1.03–2.79	74.9	0.003
Studies adjusted for prenatal alcohol and/or other drugs	Yes	16	1.28	1.18–1.40	88.0	< 0.001
	No	11	1.58	1.14–2.19	89.3	< 0.001
Studies adjusted for pre-pregnancy/ gestational hypertension and/or diabetes	Yes	12	1.36	1.21–1.53	94.6	< 0.001
	No	15	1.31	1.18–1.45	22.2	0.207
Studies adjusted for household income	Yes	8	1.35	1.28–1.44	59.1	0.017
	No	19	1.38	1.24–1.48	89.1	< 0.001
Prenatal cannabis exposure ascertained	During first trimester	5	1.45	1.10–1.89	49.2	0.096

CI = confidence interval.

between prenatal cannabis exposure and preterm birth has not changed since 2014, showing that evidence for the existence of a statistical association was sufficient from that time. Further, evidence based on the stability threshold indicated that the current statistical evidence is stable. Moreover, the association reported in this meta-analysis was not sensitive to adjustment for important confounders such as maternal prenatal exposure to alcohol, tobacco and other drugs, household income, previous preterm birth, pre-pregnancy or gestational hypertension and/or diabetes. The findings of this meta-analysis add to mounting body of evidence suggesting deleterious effects of cannabis use during pregnancy on preterm birth. The findings further support the message provided by the American College of Obstetricians and Gynaecologists [51] that pregnant mothers should be encouraged to avoid cannabis use during prenatal period to reduce such adverse birth outcomes. Although the medical use of cannabis might have health benefits, the findings of this meta-analysis clearly suggest that its use should not be encouraged during pregnancy [52].

The precise mechanism explaining the association between prenatal cannabis exposure and offspring preterm birth remains to be elucidated. However, several plausible mechanisms have been proposed. One proposed mechanism is that the toxic effects of several compounds present in cannabis can readily cross the placenta, including delta-9-tetrahydrocannabinol and cannabidiol [53]. These chemicals can result in impaired placenta development and insufficient blood circulation [54, 55]. Insufficient placental blood circulation may result in fetal growth restriction and development [56]. This, in turn, has been associated with spontaneous preterm birth [57].

Another possibility is that the association between prenatal cannabis exposure and the risk of preterm birth may be due to confounding by maternal alcohol, tobacco or other drug use during pregnancy. This interpretation is probable when considering that the estimates in our study were sensitive to adjustment for these factors. Pregnant women who reported cannabis use during pregnancy were more likely to consume alcohol, tobacco and other drugs during pregnancy [18] which, in turn, were associated with preterm birth in offspring [58–60]. An epidemiological study from the United States examined the association between preterm birth and timing and intensity of maternal prenatal tobacco smoking in a sample of more than a quarter of a million mother–infant pairs [58]. In that study, maternal tobacco smoking during the first and second trimesters of pregnancy was associated with an increased risk of preterm birth in offspring. Maternal alcohol consumption during pregnancy was also associated with an increased risk of extreme preterm birth even after adjusting for available confounders, such as the use of other substances during prenatal period, socio-demographic and clinical factors [59]. Similarly, in our meta-analysis the risk of preterm birth was substantially attenuated in the magnitude in the studies that adjusted for prenatal exposure to tobacco, alcohol and other drugs, suggesting that such exposures may have some role in the observed association. However, none of them appeared to nullify the association. This suggests such exposures were partly responsible for the increased risk in offspring pre-term birth, although slightly elevated estimates still remained after adjustment.

The association between preterm birth and prenatal cannabis use may also be due to a range of risk factors such as hypertensive disorders of pregnancy and gestational diabetes [61, 62]. Evidence from an epidemiological study has suggested that the risk of preterm birth due to gestational diabetes may be higher if pregnant women develop diabetes prior to the 24th week of gestation [62]. However, in our meta-analysis, the association between preterm birth and prenatal cannabis use was somewhat similar in the studies that did and did not adjust for pre-pregnancy hypertension/diabetes and/or gestational hypertension/diabetes.

The strengths of this meta-analysis include: the use of a predefined search strategy and data extraction protocol which was prospectively registered in the PROSPERO database; the ability to conduct subgroup and sensitivity analysis based on different risk factors including maternal substance use during pregnancy to further explore the source of heterogeneity throughout included studies; the methodological quality appraisal of studies included in the meta-analysis was evaluated by two independent reviewers to minimize potential reviewer bias; and cumulative meta-analysis and stability threshold were also conducted to investigate how the pooled estimate and its precision changes over time. The implication of our stability threshold findings is that whether an association exists among observational epidemiological studies is currently less relevant an objective for future studies than characterizing risk. More specifically, the focus of observational research can now shift to more clearly understand biological pathways and estimate the magnitude of risk (particularly in biologically susceptible and marginalized vulnerable populations) and to consider strategies for intervention and prevention. However, several caveats need to be considered when interpreting and generalizing the findings of this cumulative meta-analysis. Prenatal cannabis exposure cannot be ethically randomized to participants during pregnancy, and therefore all studies adopted observational designs. The stability threshold indicates that the pooled result from these observational studies is stable, but this pooled result is not necessarily the same as the pooled estimate that would have been obtained from hypothetical randomized experiments. We cannot exclude the possibility of systematic bias among some or all of the individual observational studies. Continued examination of the influence of potential bias is warranted. A limitation of this study was that we could not conduct additional sensitivity analyses based on dose–response associations due to lack of sufficient and consistent data from the included studies. Due to the inconsistencies in reporting among studies we could not compute trimester-specific estimates. Although the level of adjustment for potential confounders and covariates was inconsistent throughout studies, we noted positive associations in the studies that comprehensively controlled for potential confounders and socio-demographic covariates and for the studies that partially adjusted for these covariates. Most of the studies included in the current review contained no information regarding smoking cessation. Consequently, a significant proportion of women classified as non-smokers may have smoked up until the time that they became aware of their pregnancy. Conversely, a significant proportion of women classified as smokers may have not smoked after becoming aware of their pregnancy.

The findings of this cumulative meta-analysis indicate that the women in these studies who reported consumption of cannabis during pregnancy were more likely to deliver preterm birth, which warrants public health messages to avoid such exposure, particularly during pregnancy.

ETHICS STATEMENT

This study was conducted in compliance with principles outlined in the Declaration of Helsinki. Ethical committee approval for this study was not required.

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DECLARATION OF INTERESTS

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

AUTHOR CONTRIBUTIONS

BD conceived the hypothesis, developed the methodology, identified all potential studies, extracted the data, assessed methodological quality of individual study, conducted data analysis, and wrote the first draft of the manuscript. BDA conducted data extraction and quality appraisal of the included studies. GP assisted and computed stability thresholds. BDA, GP, and RA contributed to the design of the study; reviewed the methodology, data analysis, and interpretations of the results; and contributed to critical revisions of the subsequent drafts of the manuscript for important intellectual content. All authors read and approved the final manuscript.

DATA AVAILABILITY STATEMENT

All data generated or analysed during this cumulative meta-analysis were included in this article and are attached as Supporting information.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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