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Cannabis Use in Pregnancy and Neonatal Outcomes: A Systematic Review and Meta-Analysis

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Abstract

Objective: To determine whether prenatal cannabis use alone increases the likelihood of fetal and neonatal morbidity and mortality.

Study Design: We searched bibliographic databases, such as PubMed, Embase, Scopus, Cochrane reviews, PsycInfo, MEDLINE, Clinicaltrials.gov, and Google Scholar from inception through February 14, 2022. Cohort or case–control studies with prespecified fetal or neonatal outcomes in pregnancies with prenatal cannabis use. Primary outcomes were preterm birth (PTB; <37 weeks of gestation), small-for-gestational-age (SGA), birthweight (grams), and perinatal mortality. Two independent reviewers screened studies. Studies were extracted by one reviewer and confirmed by a second using a predefined template. Risk of bias assessment of studies, using the Newcastle–Ottawa Quality Assessment Scale, and Grading of Recommendations Assessment, Development, and Evaluation for evaluating the certainty of evidence for select outcomes were performed by two independent reviewers with disagreements resolved by a third. Random effects meta-analyses were conducted, using adjusted and unadjusted effect estimates, to compare groups according to prenatal exposure to cannabis use status.

Results: Fifty-three studies were included. Except for birthweight, unadjusted and adjusted meta-analyses had similar results. We found very-low- to low-certainty evidence that cannabis use during pregnancy was significantly associated with greater odds of PTB (adjusted odds ratio [aOR], 1.42; 95% confidence interval [CI], 1.19 to 1.69; I^2, 93%; $p = 0.0001$), SGA (aOR, 1.76; 95% CI, 1.52 to 2.05; I^2, 86%; $p < 0.0001$), and perinatal mortality (aOR, 1.5; 95% CI, 1.39 to 1.62; I^2, 0%; $p < 0.0001$), but not significantly different for birthweight (mean difference, −40.69 g; 95% CI, −124.22 to 42.83; I^2, 85%; $p = 0.29$). Because of substantial heterogeneity, we also conducted a narrative synthesis and found comparable results to meta-analyses.

Conclusion: Prenatal cannabis use was associated with greater odds of PTB, SGA, and perinatal mortality even after accounting for prenatal tobacco use. However, our confidence in these findings is limited. Limitations of most existing studies was the failure to not include timing or quantity of cannabis use. This review can help guide health care providers with counseling, management, and addressing the limited existing safety data.

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Introduction

With increasing legalization, prenatal cannabis use has substantially increased, and cannabis is now the most common federally illegal drug used in pregnancy.[1–4] The potency of cannabis also nearly tripled over the last two decades.[5] Approximately half of pregnant individuals who use cannabis continue to use throughout pregnancy, particularly in the first trimester during organogenesis when the fetus is most sensitive to adversity.[4,6–10]

Although the American College of Obstetricians and Gynecologists has advised pregnant and lactating individuals to abstain from cannabis, most continue to use partly because current safety data are limited.[1,11–13] There is concern for detrimental fetal and offspring outcomes[14–16] because cannabis' main active component, delta-9-tetrahydrocannabinol, readily crosses the placenta. The limited available evidence suggests that prenatal cannabis exposure is associated with stillbirth, intrauterine growth restriction, and impaired fetal neurodevelopment.[15–22]

Prior studies examining the association between prenatal cannabis use and adverse outcomes, including the most recently published systematic review and meta-analysis,[23] are largely limited by lack of statistical adjustment for important confounding factors, especially prenatal tobacco use. A prior meta-analysis noted that significant associations between prenatal cannabis use and higher rates of low birthweight (LBW) and preterm delivery dissipated after adjustment for prenatal tobacco use.[24] However, most studies included in that meta-analysis collected data before state-level recreational cannabis legalization. Indeed, patterns of cannabis use have changed in recent years, and the potency of cannabis itself has increased.[5]

As cannabis has become more potent and perceived risk has declined, prenatal use has increased.[1,2,4,5] The purpose of this systematic review and meta-analysis is to provide a contemporary understanding of the association, after accounting for tobacco use, between prenatal cannabis exposure and fetal and neonatal outcomes.

Methods

We conducted this review using standard systematic review methods and reported our findings using the Meta-analysis of Observational studies in Epidemiology (MOOSE) reporting guidelines. This review was conducted as part of the Systematically Testing the Evidence on Marijuana project, which is funded by the Veterans Health Administration's Office of Rural Health and is intended to help health care providers have evidence-informed discussions about cannabis with patients (www.cannabisevidence.org). As part of this project, we will conduct literature surveillance and update findings for this review at least once yearly.

Information sources and search strategy

We performed systematic searches of MEDLINE (Ovid), CINAHL (EBSCOHost), PsycInfo (Ovid), Global Health (Ovid), and EBM Reviews Cochrane Database of Systematic Reviews (Ovid) from database inception through February 14, 2022, based on a predesigned protocol registered with PROSPERO (CRD42020172343). An experienced research librarian developed the search strategies, which were peer reviewed by a second research librarian using the Peer Review of Search Strategies instrument.[25] Reference lists of included studies and relevant systematic reviews and meta-analyses were reviewed for additional publications of interest. Full search strategies are available in the Supplementary Data. The MOOSE reporting guidelines were followed.

Study selection

Studies were eligible if they (1) were published in a peer-reviewed scientific journal, (2) included pregnant individuals up to 1 year postdelivery; (3) included individuals for whom cannabis was the only illicit substance used during pregnancy; (4) used a cohort or case–control study design; (5) had a comparator group of noncannabis users, or lower dose or frequency users; (6) assessed 1 or more outcomes of interest; and (7) adjusted for prenatal tobacco, alcohol, and polysubstance use in statistical models.

Only English-language studies were included. The definition of cannabis exposure during pregnancy included any amount, duration, or frequency and was defined by self-report, toxicology results, or both depending on the individual study. Although toxicology testing is a more objective and precise method to ascertain prenatal cannabis use, self-report was also included due to the limited number of studies using toxicology alone. Primary outcomes were preterm birth (PTB; < 37 weeks of gestation), birthweight, perinatal mortality, and small-for-gestational-age (SGA; weight < 10th percentile given gestational age and sex of offspring).

Secondary outcomes were gestational age, LBW (< 2500 g), neonatal intensive care unit (NICU)

admissions, and Apgar score at 1 and 5 min. These outcomes were selected because they are the most evaluated outcomes in the literature and are most relevant to pregnant individuals and clinicians.

Data extraction

From each study, we abstracted details on study design, setting, duration, ascertainment of cannabis use, comparators, participant characteristics, and outcomes. Data were abstracted by one reviewer and confirmed by a second.

Risk of bias of included studies

Two independent reviewers assessed each trial for inclusion at the title and abstract and full-text levels. Two independent reviewers also assessed the risk of bias (RoB) for included studies using the Newcastle–Ottawa Scale (NOS).[26] The NOS ranges from 1 to 9 stars. For ease in interpretation and because the Cochrane Collaboration advises against use of summary numeric scores for RoB,[27] we categorized the numeric ratings as "low" (7–9), "moderate" (4–6), and "high" (1–3) RoB. Disagreements were resolved by consensus or a third reviewer. Unpublished studies and conference abstracts were included in our search, but excluded from our analysis as it has been shown that their exclusion does not change the precision or accuracy of the results.[28]

Certainty of evidence

Two independent raters assigned a summary judgment for the overall certainty of evidence (CoE) for each primary outcome, using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach.[29] Disagreements were resolved by consensus. Because it would be unethical to evaluate cannabis use in pregnancy through randomized trials, observational evidence (e.g., cohort studies) will be the highest quality study design data derived for this topic. As a result, we started all outcomes at high CoE, pulling from recent guidance by the GRADE working group about nonrandomized studies evaluating interventions.[30] We downgraded each outcome one level for internal validity concerns (RoB), such as a lack of randomization and vulnerability to confounding.

Data synthesis

For our data synthesis, we conducted an overall qualitative synthesis of all eligible studies for our four primary outcomes (PTB, birthweight, perinatal mortality, and SGA). Then, for studies that reported sufficient data for quantitative syntheses, we conducted meta-analyses of those studies reporting unadjusted effect size estimates, followed by separate meta-analyses of those reporting adjusted effect sizes for each of our primary outcomes. We conducted both qualitative and quantitative analyses because of variation in how data were reported in eligible studies and statistical heterogeneity we detected in our meta-analyses.

For the meta-analyses of unadjusted effect sizes, we first calculated effect size estimates using study-reported within-group results (e.g., means and standard deviations [SDs] for continuous outcomes and counts of individuals with events for binary outcomes). For birthweight, we calculated mean differences (MDs) and 95% confidence intervals (CIs) between the exposed and unexposed groups. For PTB, perinatal mortality, and SGA, we calculated odds ratios (ORs) and 95% CIs, reflecting the relative odds of a participant experiencing an event between the exposed and unexposed groups.
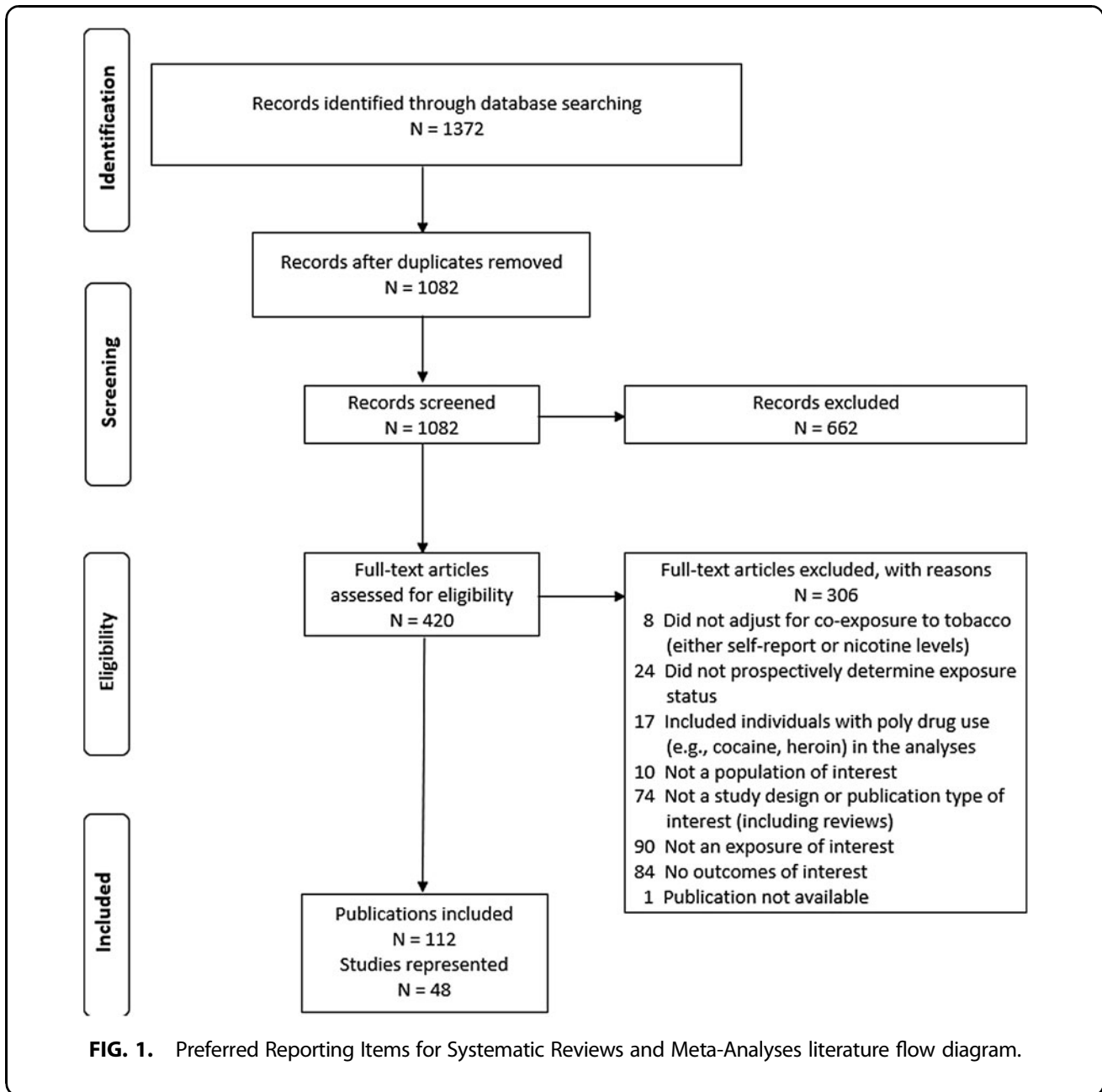
We additionally conducted meta-analyses using study-reported effect size estimates that had been adjusted for confounding variables (e.g., smoking, alcohol use, race/ethnicity) for outcomes for which three or more studies reported the same type of effect size (e.g., MD, OR). For studies that reported adjusted effect sizes stratified by subgroups of cannabis use frequency, we incorporated each of the subgroups using multilevel models to account for the within-study dependency (e.g., correlated error) introduced by including multiple comparisons within a single study.

We used DerSimonian–Laird random effects models to synthesize effect estimates, and evaluated statistical heterogeneity using prediction intervals and the I^2 statistic.[31] All analyses were conducted using the meta package in R, version 4.0.3 (R Project for Statistical Computing).[32]

Results

Overall characteristics of studies

The study selection process is depicted in Figure 1. After reviewing 1902 titles and abstracts, we included a total of 53 studies from 127 publications. Table 1 describes the studies' characteristics. We found 1 case–control study[18] and 52 cohort studies; 31 studies were published after 2012, the year cannabis was first legalized for recreational use in Colorado and Washington. Table 2 describes the quality of included

FIG. 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses literature flow diagram.

studies. We assessed 3 studies[33–35] as having a moderate RoB, and 50 studies as low RoB. The included studies largely consisted of pregnant individuals who identified as non-Hispanic Black, Hispanic, or non-Hispanic White, were typically 20 to 30 years of age, had completed high school or less, and had received some form of prenatal care (Supplementary Table S1). Study participants varied in when and how often they used tobacco during pregnancy, with cannabis-using participants being more likely to use tobacco than noncannabis-using participants.

The included studies varied in how cannabis exposure was defined; some studies included only participants with regular and continued use, while others included individuals with irregular use or who discontinued use during pregnancy. Most studies relied on self-reported exposure to cannabis, while some used toxicology results or both, and few used umbilical cord or meconium testing for confirmation. Five studies[35–39] used administrative databases to compare those with cannabis-related disorders to those with no diagnosis codes related to cannabis use. Studies were generally conducted in the

Table 1. Included Study Characteristics

Study	Year	Study design	RoB	Location	Total, N	Participants by group, %	MJ use ascertainment	Outcomes
Koto et al[50]	2022	Retrospective cohort	Low	Canada	106,282	MJ use: 2.9 Unexposed: 97.1	Self-report	PTB, birthweight, SGA, GA, NICU, 5 min APGAR
Oni et al[36]	2022	Retrospective cohort	Low	Australia	622,640	MJ use, CUD: 0.3 Unexposed: 99.7	Diagnostic code	PTB, perinatal death, LBW, NICU, 1 min APGAR, 5 min APGAR
Bandoli et al[37]	2021	Retrospective cohort	Low	United States	3,067,069	MJ use alone: 0.5 MJ use + tobacco: 0.2 Unexposed: 99.1	Diagnostic code	PTB, SGA, NICU
Bruno et al[35]	2021	Prospective cohort	Moderate	United States	9509	MJ use: 1.5 Unexposed: 98.5	Self-report, Tox screen	SGA
Sasso et al[51]	2021	Retrospective cohort	Low	United States	362	MJ use: 44.0 Unexposed: 56.0	Self-report, Tox screen	PTB, birthweight, SGA, perinatal death, GA, NICU, 5 min APGAR
Bailey et al[52]	2020	Retrospective cohort	Low	United States	1062	MJ use: 50.0 Unexposed: 50.0	Tox screen	PTB, birthweight, LBW, GA, NICU, 1 min APGAR, 5 min APGAR
Gabrhelik et al[53]	2020	Prospective cohort	Low	Norway	10,373	MJ use, short-term: 2.0 MJ use, long-term: 0.6 Unexposed: 97.4	Self-report	PTB, birthweight, SGA, NICU, 1 min APGAR, 5 min APGAR
Klebanoff et al[54]	2020	Prospective cohort	Low	United States	363	MJ use: 32.8 Unexposed: 67.2	Self-report, Tox screen	PTB, birthweight, LBW, GA
Lee et al[55]	2020	Retrospective cohort	Low	United States	466	MJ use: 9.7 Unexposed: 9.0	Tox screen	PTB, birthweight, SGA, perinatal mortality, GA, NICU, 1 min APGAR
Wong et al[56]	2020	Retrospective cohort	Low	Canada	25,263	MJ use: 2.2 Unexposed: 97.8	Self-report	PTB, LBW, 5 min APGAR
Corsi et al[49]	2019	Retrospective cohort	Low	Canada	98,512	MJ use: 5.7 Unexposed: 94.3	Self-report	PTB, SGA, perinatal mortality, NICU, 5 min APGAR
Howard et al[57]	2019	Retrospective cohort	Low	United States	2173	MJ use, intake visit: 16.0 MJ use, delivery: 1.2 MJ use, intake + delivery: 5.3 Unexposed: 77.5	Tox screen	Birthweight, perinatal mortality, GA, 1 min APGAR, 5 min APGAR
Kharbanda et al[58]	2019	Retrospective cohort	Low	United States	3435	MJ use: 8.2 Unexposed: 91.8	Tox screen	PTB, SGA, LBW
Luke et al[59]	2019	Retrospective cohort	Low	Canada	243,140	MJ use: 2.4 Unexposed: 97.6	Self-report	PTB, SGA, perinatal mortality
Petrangelo et al[38]	2019	Retrospective cohort	Low	United States	12,578,557	MJ use, CUD: 0.5 Unexposed: 99.5	Diagnostic code	PTB, perinatal death
Rodriguez et al[60]	2019	Retrospective cohort	Low	United States	1206	MJ use: 17.5 Unexposed: 82.5	Self-report, Tox screen	PTB, birthweight, SGA, perinatal death, GA, NICU, 5 min APGAR
Straub et al[61]	2019	Retrospective cohort	Low	United States	5343	MJ use: 23.7 Unexposed: 76.3	Tox screen	PTB, birthweight, SGA, LBW, GA
Wall et al[62]	2019	Prospective cohort	Low	United States	803	MJ use: 17.4 Unexposed: 82.6	Self-report	Perinatal death
Coleman-Cowger et al[63]	2018	Prospective cohort	Low	United States	414	MJ use: 14.5 Unexposed: 85.5	Self-report, Tox screen	PTB, perinatal death, LBW, NICU
Massey et al[64]	2018	Retrospective cohort	Low	United States	1191	MJ use: 22.9 Unexposed: 77.1	Self-report, Tox screen, Meconium	Birthweight, GA
Serino et al[65]	2018	Prospective cohort	Low	United States	87	MJ use: 26.0 Unexposed: 33.6	Self-report, Tox screen	Birthweight, GA, 5 min APGAR
Dotters-Katz et al[66]	2017	Retrospective cohort	Low	United States	1867	MJ use: 7.3 Unexposed: 92.7	Self-report, Tox screen	PTB, birthweight, SGA, perinatal death, GA, 5 min APGAR

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Table 1. Continued

Study	Year	Study design	RoB	Location	Total, N	Participants by group, %	MJ use ascertainment	Outcomes
Chabarria et al[67]	2016	Retrospective cohort	Low	United States	12,069	MJ use: 0.5 Unexposed: 97.5	Self-report	PTB, SGA, LBW, 5 min APGAR
Leemaqz et al[68]	2016	Prospective cohort	Low	Australia, New Zealand, United Kingdom, Ireland	5588	MJ use, < 15 weeks GA: 2.6 MJ use, 15 weeks GA: 1.1 MJ use, <20 weeks GA: 0.4 MJ use, 20 weeks GA: 1.0 Unexposed: 94.4 1.7% quit MJ before pregnancy	Self-report	PTB, birthweight, SGA, GA
Mark et al[69]	2016	Retrospective cohort	Low	United States	396	MJ use: 29.3 Unexposed: 70.7	Self-report, Tox screen	PTB, birthweight, LBW, GA, NICU, 1 min APGAR, 5 min APGAR
Conner et al[24]	2015	Retrospective cohort	Low	United States	8138	MJ use: 8.4 Unexposed: 91.6	Self-report, Tox screen	LBW, NICU, 5 min APGAR
Grewen et al[33]	2015	Prospective cohort	Moderate	United States	63	MJ use: 31.7 Unexposed: 31.7	Self-report, Tox screen, Meconium	Birthweight, GA
Warshak et al[70]	2015	Retrospective cohort	Low	United States	6468	MJ use: 5.6 Unexposed: 94.4	Self-report, Tox screen	PTB, SGA, perinatal death, GA, NICU
Bonello et al[39]	2014	Retrospective cohort	Low	Australia	13,480	MJ use, CUD: 2.7 Unexposed: 97.3	Diagnostic code	PTB, LBW, NICU
Varner et al[18]	2014	Case–control	Low	United States	1610	MJ use: 3.0 Unexposed: 97.0	Self-report, umbilical cord	PTB, SGA, perinatal death, GA, NICU
Alhusen et al[17]	2013	Prospective cohort	Low	United States	166	MJ use: 38.5 Unexposed: 61.4	Self-report	PTB, SGA, LBW
Hayatbakhsh et al[19]	2011	Retrospective cohort	Low	Australia	24,874	MJ use: 2.6 Unexposed: 97.4	Self-report	PTB, birthweight, SGA, LBW, GA, NICU, 5 min APGAR
Gray et al[71]	2010	Prospective cohort	Low	United States	86	MJ use: 44.2 Unexposed: 55.8	Self-report, Tox screen, Meconium	PTB, birthweight, GA, 1 min APGAR, 5 min APGAR
Schempf et al[72]	2008	Retrospective cohort	Low	United States	808	MJ use: 15.2 Unexposed: 84.8	Self-report, Tox screen	Birthweight, LBW
Lozano et al[73]	2007	Prospective cohort	Low	Spain	974	MJ use: 5.3 Unexposed: 89.9	Meconium	PTB, birthweight
Burns et al[74]	2006	Retrospective cohort	Low	Australia	416,834	MJ use, CUD: 0.5 Unexposed: 99.0	Diagnostic code	PTB, SGA, NICU, 5 min APGAR
Bada et al[75]	2005	Prospective cohort	Low	United States	8637	MJ use: 9.4 Unexposed: 90.6	Self-report, Meconium	PTB, birthweight, LBW
Reichman et al[76]	2003	Retrospective cohort	Low	United States	90,117	MJ use: 2.4 Unexposed: 91.8	Self-report	PTB, birthweight, LBW, GA
Fergusson et al[14]	2002	Prospective cohort	Low	England	12,129	MJ use NR by group	Self-report	PTB, birthweight, perinatal mortality, NICU
Quinlivan et al[77]	2002	Prospective cohort	Low	Australia	456	MJ use: 13.6 Unexposed: 79.6	Self-report	PTB, birthweight, GA, 1 min APGAR, 5 min APGAR
Sherwood et al[34]	1999	Retrospective cohort	Moderate	United Kingdom	283	MJ use: 11.0 Unexposed: 89.0	Tox screen	Birthweight, perinatal mortality, GA, 5 min APGAR
Berenson et al[78]	1996	Retrospective cohort	Low	United States	238	MJ use: 38.2 Unexposed: 61.8	Tox screen	LBW, NICU, 1 min APGAR, 5 min APGAR
Cornelius et al[79]	1995	Prospective cohort	Low	United States	310	MJ use: 17.7 Unexposed: 82.3	Self-report	Birthweight, SGA, LBW, GA
Shiono et al[47]	1995	Prospective cohort	Low	United States	7470	MJ use: 11.0 Unexposed: 89.0	Self-report, Tox screen	PTB, LBW

(continued)

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Table 1. Continued

Study	Year	Study design	RoB	Location	Total, N	Participants by group, %	MJ use ascertainment	Outcomes
Kliegman et al[80]	1994	Prospective cohort	Low	United States	425	NR by MJ use status	Self-report, Tox screen	PTB, LBW
Richardson et al[81]	1989	Prospective cohort	Low	United States	519	MJ use, heavy use 1st trimester: 19.9 MJ use, heavy use 2nd trimester: 7.3 MJ use, heavy use 3rd trimester: 7.1 Unexposed: 40.5	Self-report	Birthweight, GA
Hayes et al[82]	1988	Prospective cohort	Low	Jamaica	56	MJ use, irregular: 19.6 MJ use, moderate: 19.6 MJ use, heavy: 14.3 Unexposed: 46.5	Self-report	PTB, birthweight, perinatal mortality, GA
Kline et al[83]	1987	Retrospective cohort	Low	United States	Phase 1: 1432 Phase 2: 1377	Phase 1 MJ use, ≤1/month: 4.7 MJ use, 2–4/month: 1.9 MJ use, 2–3/week: 1.3 MJ use, 4–6/week: 0.4 MJ use, daily: 1.0 Unexposed: 90.7 Phase 2 MJ use, ≤1/month: 2.9 MJ use, 2–4/month: 1.7 MJ use, 2–3/week: 2.1 MJ use, 4–6/week: 0.5 MJ use, daily: 3.1 Unexposed: 89.7	Self-report	Birthweight
Hatch et al[84]	1986	Prospective cohort	Low	United States	3857	MJ use, ≤1 per month: 4.1 MJ use, >1 per month: 5.4 Unexposed: 90.5	Self-report	PTB, birthweight, SGA, LBW, GA
Tennes et al[85]	1985	Prospective cohort	Low	United States	756	MJ use: 34.1 Unexposed: 65.9	Self-report	PTB, birthweight, GA
Gibson et al[86]	1983	Prospective cohort	Low	Australia	7310	MJ use, ≤weekly: 4.9 MJ use, >weekly: 0.5 Unexposed: 94.6	Self-report	PTB, perinatal mortality, LBW, 1 min APGAR
Greenland et al[87]	1982	Prospective cohort	Low	United States	71	MJ use: 49.3 Unexposed: 50.7	Self-report, Tox screen, Umbilical cord	PTB, LBW, 5 min APGAR
Fried et al[88]	1980	Prospective cohort	Low	Canada	Initial cohort: 291 Updated cohort: 583	Initial cohort MJ use, heavy: 3.8 MJ use, moderate: 1.7 MJ use, irregular: 14.1 Unexposed: 80.4 Updated cohort MJ use, heavy: 3.1 MJ use, moderate: 3.1 MJ use, irregular: 8.2 Unexposed: 85.6	Self-report	PTB, birthweight, GA

APGAR, appearance, pulse, grimace, activity, respiration; CUD, cannabis use disorder; GA, gestational age; LBW, low birthweight; MJ, marijuana; NICU, neonatal intensive care unit; NR, not reported; PTB, preterm birth; RoB, risk of bias; SGA, small-for-gestational-age.

Table 2. Summary of Findings for Cannabis Use During Pregnancy and Perinatal Outcomes

Outcome. number of studies, sample size	Findings (unadjusted and adjusted)	CoE	Relationship	Rationale
Birthweight (mean) 31 studies (narrative synthesis) $N = 282,699$	Unadjusted MD, -141.62; 95% CI, -192.04 to -91.19 Based on 22 studies with 174,638 participants Adjusted MD, -40.69; 95% CI, -124.22 to 42.83 Based on 4 studies (8 comparisons) with 33,299 participants	Low	Unclear relationship between cannabis use in pregnancy and birthweight	Downgraded 1 level each for risk of bias (if compared with a target RCT) and inconsistency (high levels of heterogeneity between studies)
PTB (<37 weeks) 41 studies (narrative synthesis) $N = 17,943,871$	Unadjusted OR, 1.62; 95% CI, 1.43 to 1.83 Based on 31 studies with 14,297,813 participants Adjusted OR, 1.42; 95% CI, 1.19 to 1.69 Based on 12 studies with 13,928,094 participants	Low	After adjustment, increased odds of PTB with use of cannabis during pregnancy	Downgraded 1 level each for risk of bias (if compared with a target RCT) and inconsistency (high levels of heterogeneity between studies)
Perinatal mortality (e.g., stillbirth, fetal demise) 17 studies (narrative synthesis) $N = 14,141,101$	Unadjusted OR, 1.84; 95% CI, 1.47 to 2.29 Based on 12 studies with 13,508,621 participants Adjusted OR, 1.50; 95% CI, 1.39 to 1.62 Based on 5 studies with 13,206,209 participants	Very low	After adjustment, increased odds of perinatal mortality with use of cannabis during pregnancy	Downgraded 1 level for risk of bias (if compared with a target RCT) and 2 levels for indirectness (the adjusted analysis was based primarily on a study using ICD codes, with a weight of 95.2%, likely to be assigned only to individuals with moderate-to-heavy cannabis use during pregnancy, and not to occasional users)
SGA (<10th percentile given sex and gestational age) 21 studies (narrative synthesis) $N = 4,582,445$	Unadjusted OR, 2.06; 95% CI, 1.76 to 2.41 Based on 18 studies with 1,774,485 participants Adjusted OR, 1.76; 95% CI, 1.52 to 2.06 Based on 6 studies with 686,336 participants	Low	After adjustment, increased odds of SGA birth with cannabis use during pregnancy	Downgraded 1 level each for risk of bias (if compared with a target RCT) and inconsistency (high levels of heterogeneity between studies)

Note: We started the CoE as high, with downgrading, if compared with a target RCT, as outlined in the Grading of Recommendations Assessment, Development, and Evaluation guidelines.[30]
CI, confidence interval; CoE, certainty of evidence; ICD, international classification of diseases; MD, mean difference; OR, odds ratio; RCT, randomized controlled trial.

United States; publication dates ranged from 1980 to 2022, spanning a period characterized by a significant increase in cannabis potency, emergence of different cannabis strains and routes of administration, and legalization that can influence accuracy of participant self-report.
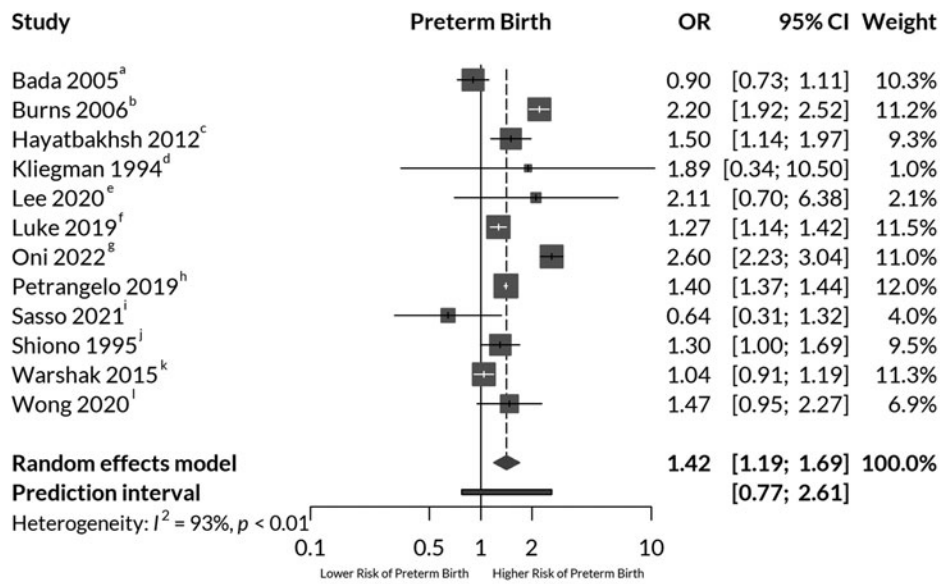
Primary outcomes
PTB (<37 weeks). Overall, we identified 41 studies ($N = 17,943,871$) examining the association of prenatal cannabis use and PTB (Supplementary Table S2). Of those 41 studies, 31 studies had sufficient data to conduct a meta-analysis of unadjusted effect sizes and 12 had sufficient data to conduct a meta-analysis of adjusted effect sizes. Generally, studies reported results for any PTB; however, a small number of studies stratified results by spontaneous versus indicated PTBs. Across the 41 studies,

we typically observed that cannabis use in pregnancy was associated with an increased likelihood of PTB.

In our unadjusted meta-analysis (31 studies; $N = 14,297,813$), we also found that cannabis use in pregnancy increased the odds of PTB (OR, 1.62; 95% CI, 1.43 to 1.83; Supplementary Fig. S1). There were very similar findings among the 12 studies ($N = 13,928,094$) that reported adjusted data for a meta-analysis (adjusted odds ratio [aOR], 1.42; 95% CI, 1.19 to 1.69; I^2, 93%; Fig. 2). We rated the CoE for PTB as low and downgraded it for inconsistency (differences in magnitude of association between studies) and RoB (if compared with a target randomized controlled trial; Table 2).

Birthweight. We identified 31 eligible studies ($N = 282,699$) that reported data on birth weight, but across all studies, there was no clear, consistent

Study	Preterm Birth	OR	95% CI	Weight
Bada 2005[a]		0.90	[0.73; 1.11]	10.3%
Burns 2006[b]		2.20	[1.92; 2.52]	11.2%
Hayatbakhsh 2012[c]		1.50	[1.14; 1.97]	9.3%
Kliegman 1994[d]		1.89	[0.34; 10.50]	1.0%
Lee 2020[e]		2.11	[0.70; 6.38]	2.1%
Luke 2019[f]		1.27	[1.14; 1.42]	11.5%
Oni 2022[g]		2.60	[2.23; 3.04]	11.0%
Petrangelo 2019[h]		1.40	[1.37; 1.44]	12.0%
Sasso 2021[i]		0.64	[0.31; 1.32]	4.0%
Shiono 1995[j]		1.30	[1.00; 1.69]	9.5%
Warshak 2015[k]		1.04	[0.91; 1.19]	11.3%
Wong 2020[l]		1.47	[0.95; 2.27]	6.9%
Random effects model		1.42	[1.19; 1.69]	100.0%
Prediction interval			[0.77; 2.61]	

Heterogeneity: $I^2 = 93\%$, $p < 0.01$

0.1 0.5 1 2 10

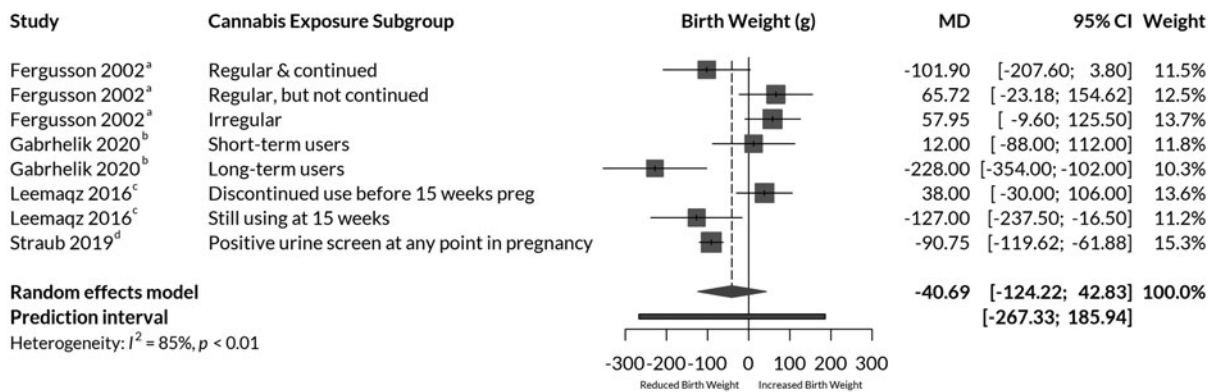Lower Risk of Preterm Birth   Higher Risk of Preterm Birth

[a]Adjusted for location; use of tobacco, alcohol, other drugs
[b]Adjusted for maternal age; indigenous status; private insurance; use of tobacco, alcohol, or other drugs
[c]Adjusted for maternal age; ethnicity; use of tobacco, alcohol, illicit drugs
[d]Adjusted for maternal age < 19; black race; staff service; no prenatal visit; primiparous; hx of PTB; hx alcohol use; hx cocaine use; cocaine toxicology
[e]Adjusted for "significant confounders"
[f]Adjusted for maternal age, pre-pregnancy BMI, tobacco use, alcohol use, other substance use, SES, and race/ethnicity
[g]Adjusted for maternal age, tobacco use, Indigenous status, health insurance, antenatal care attendance, plurality of birth, SES, pre-eclampsia, hypertension (gestational or preexisting), diabetes (gestational or preexisting), hx other substance use disorders
[h]Adjusted for age, race, hospital location or teaching, income, type of insurance, multiple pregnancy, pre-existing diabetes mellitus, tobacco use, hypertension, alcohol, and other illicit drug use
[i]Adjusted for maternal age, race, hyperemesis gravidarum, chronic hypertension, pre-eclampsia, autoimmune disease, and use of tobacco, alcohol, or illicit drugs
[j]Adjusted for tobacco use
[k]Adjusted for maternal age, race, parity, BMI class and no prenatal care
[l]Adjusted for maternal medical, behavioral, demographic, and neighborhood SES factors

FIG. 2. Adjusted meta-analyses of preterm birth after cannabis use during pregnancy. BMI, body mass index; CI, confidence interval; OR, odds ratio; SES, social economic status.

association of prenatal cannabis use with birthweight (Supplementary Table S2). Of those 31 studies, 22 studies had sufficient data to conduct a meta-analysis of unadjusted effect sizes and 4 had sufficient data to conduct a meta-analysis of adjusted effect sizes. In the few studies in which cannabis use was associated with LBW, the magnitude of difference was relatively small and potentially not clinically important ($\sim$100 to 200 g).

In our unadjusted meta-analysis of 22 studies ($N = 174{,}638$), we found that cannabis use was associated with lower mean birthweight (MD, -141.62 g; 95% CI, -192.04 to -91.19; Supplementary Fig. S2). However, in our adjusted meta-analysis (4 studies of 8 comparisons; $N = 33{,}299$), we found no evidence of an association (MD, -40.69 g; 95% CI, -124.22 to 42.83; I^2, 85%; Fig. 3). Because of the varied findings across our included studies, we rated our CoE for the association between prenatal cannabis and birthweight as low; downgrading the relationship for inconsistency and RoB (Table 2).

Study	Cannabis Exposure Subgroup	Birth Weight (g)	MD	95% CI	Weight
Fergusson 2002[a]	Regular & continued		-101.90	[-207.60; 3.80]	11.5%
Fergusson 2002[a]	Regular, but not continued		65.72	[-23.18; 154.62]	12.5%
Fergusson 2002[a]	Irregular		57.95	[-9.60; 125.50]	13.7%
Gabrhelik 2020[b]	Short-term users		12.00	[-88.00; 112.00]	11.8%
Gabrhelik 2020[b]	Long-term users		-228.00	[-354.00; -102.00]	10.3%
Leemaqz 2016[c]	Discontinued use before 15 weeks preg		38.00	[-30.00; 106.00]	13.6%
Leemaqz 2016[c]	Still using at 15 weeks		-127.00	[-237.50; -16.50]	11.2%
Straub 2019[d]	Positive urine screen at any point in pregnancy		-90.75	[-119.62; -61.88]	15.3%
Random effects model			-40.69	[-124.22; 42.83]	100.0%
Prediction interval				[-267.33; 185.94]	

Heterogeneity: I^2 = 85%, p < 0.01

-300 -200 -100 0 100 200 300
Reduced Birth Weight   Increased Birth Weight

[a]Adjusted for maternal age, height, weight, education level, ethnicity, and use of tobacco, alcohol, tea, coffee, hard drugs; parity; infant sex
[b]Adjusted for maternal age, education level, anxiety/depression, and use of tobacco, alcohol, illicit drugs, prescription drugs; parity; infant sex; whether pregnancy was planned.
[c]Adjusted for maternal age, BMI, SEI score, ethnicity, anxiety/depression, and use of tobacco, alcohol, or illicit drugs; country; infant sex; gestational age
[d]Adjusted for maternal age, BMI, ethnicity, and use of tobacco, alcohol, or illicit drugs; infant sex; gestational age; WIC enrollment, Medicaid enrollment; preterm birth

FIG. 3. Adjusted meta-analyses of offspring birthweight after cannabis use during pregnancy. MD, mean difference; SEI, socioeconomic index; WIC, Special Supplemental Nutrition Program for Women, Infants, and Children.
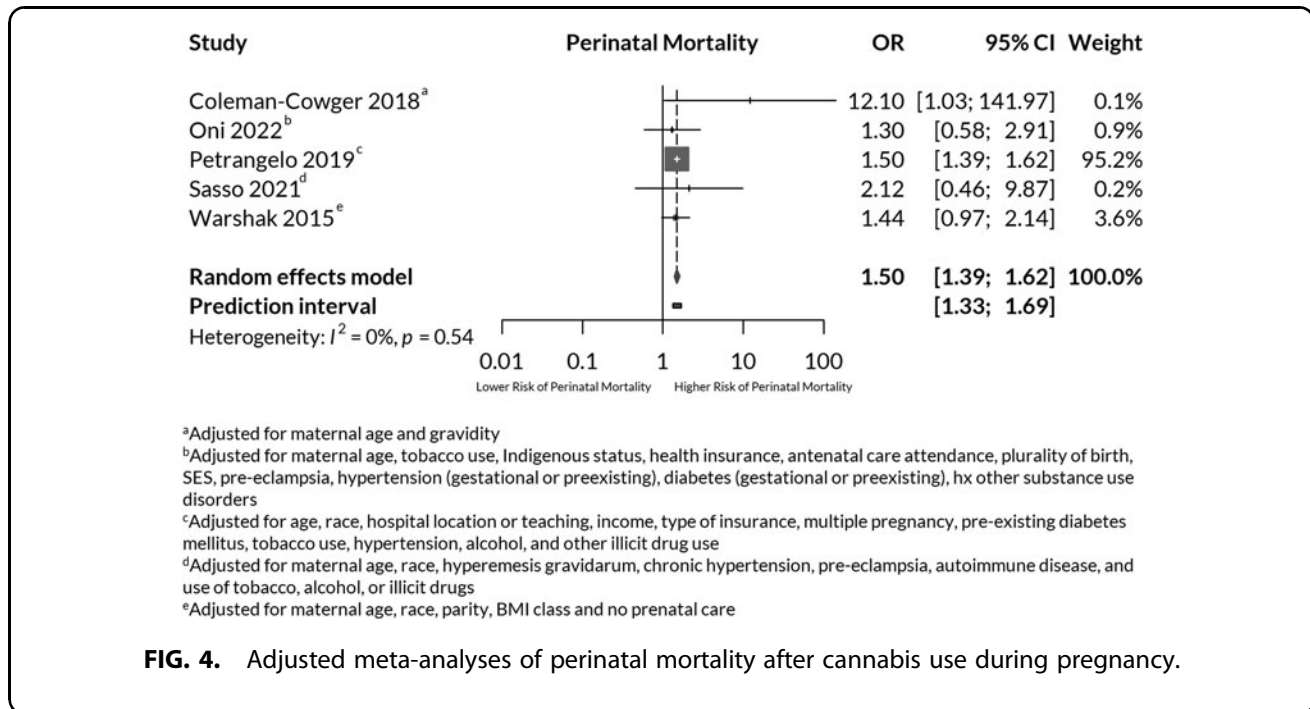
Perinatal mortality. We identified 17 eligible studies (N = 14,141,101) that analyzed the association between prenatal cannabis use and perinatal mortality (Supplementary Table S3). Of those 17 studies, 12 studies had sufficient data to conduct a meta-analysis of unadjusted effect sizes and 5 had sufficient data to conduct a meta-analysis of adjusted effect sizes. The definition of perinatal mortality varied across studies. Some studies defined it as stillbirth, while others included miscarriage/spontaneous abortion or death before hospital discharge.

The general incidence of perinatal mortality ranged from 1% to 3% of the study samples. In our narrative synthesis of included studies, we found no consistent association as most studies were likely inadequately powered to detect a significant difference between groups. Studies that observed a difference commonly had statistical imprecision (i.e., wide CIs). In our unadjusted meta-analysis (12 studies; N = 13,508,621), we observed that prenatal cannabis was significantly associated with increased odds of perinatal mortality (OR, 1.84; 95% CI, 1.47 to 2.29; Supplementary Fig. S3).

Sufficient data were present to include five studies (N = 13,206,209) in an adjusted meta-analysis, and our findings remained consistent with increased odds of perinatal mortality among those who used cannabis in pregnancy (OR, 1.50; 95% CI, 1.39 to 1.62; I^2, 0%; Fig. 4). One study,[38] with a weight of 95.2% in the meta-analysis, found that mothers reporting cannabis dependence or abuse, identified by international classification of diseases (ICD)-9 codes, were more likely to have an intrauterine fetal demise (OR 1.50; 95% CI 1.39 to 1.62). The overall incidence of perinatal mortality was 1.4%. The ICD-9 codes chosen were likely to be assigned only to individuals with moderate-to-heavy cannabis use during pregnancy, but not to occasional users. Ultimately, we have very low CoE that prenatal cannabis use increases the odds of perinatal mortality. We downgraded this evidence for RoB concerns and an additional two levels for indirectness, as the adjusted analysis was based primarily on the study using ICD-9 codes[38] (Table 2).

Small for gestational age. We identified 21 eligible studies (N = 4,582,445) that analyzed the association of prenatal cannabis use and SGA (Supplementary Table S3). Of those 21 studies, 18 studies had sufficient data to conduct a meta-analysis of unadjusted effect sizes and 6 had sufficient data to conduct a meta-analysis of adjusted effect sizes. Because SGA is defined as having a birthweight less than the 10th percentile, given sex and gestational age of the offspring, the

Study	Perinatal Mortality	OR	95% CI	Weight
Coleman-Cowger 2018[a]		12.10	[1.03; 141.97]	0.1%
Oni 2022[b]		1.30	[0.58; 2.91]	0.9%
Petrangelo 2019[c]		1.50	[1.39; 1.62]	95.2%
Sasso 2021[d]		2.12	[0.46; 9.87]	0.2%
Warshak 2015[e]		1.44	[0.97; 2.14]	3.6%
Random effects model		1.50	[1.39; 1.62]	100.0%
Prediction interval			[1.33; 1.69]	

Heterogeneity: $I^2 = 0\%$, $p = 0.54$

0.01 0.1 1 10 100

Lower Risk of Perinatal Mortality   Higher Risk of Perinatal Mortality

[a]Adjusted for maternal age and gravidity
[b]Adjusted for maternal age, tobacco use, Indigenous status, health insurance, antenatal care attendance, plurality of birth, SES, pre-eclampsia, hypertension (gestational or preexisting), diabetes (gestational or preexisting), hx other substance use disorders
[c]Adjusted for age, race, hospital location or teaching, income, type of insurance, multiple pregnancy, pre-existing diabetes mellitus, tobacco use, hypertension, alcohol, and other illicit drug use
[d]Adjusted for maternal age, race, hyperemesis gravidarum, chronic hypertension, pre-eclampsia, autoimmune disease, and use of tobacco, alcohol, or illicit drugs
[e]Adjusted for maternal age, race, parity, BMI class and no prenatal care

FIG. 4. Adjusted meta-analyses of perinatal mortality after cannabis use during pregnancy.

expected occurrence of SGA is 10%. However, most studies reported higher proportion of events, particularly in the exposure groups. In our narrative synthesis, we observed a trend of prenatal cannabis use significantly increasing the likelihood of SGA.

Similarly, in our unadjusted (18 studies; $N =$ 1,774,485) and adjusted (6 studies; 686,336) meta-analyses, prenatal cannabis use significantly increased the odds of SGA (unadjusted OR, 2.06; 95% CI, 1.76 to 2.41; aOR, 1.76; 95% CI, 1.52 to 2.05; I^2, 86%; Supplementary Fig. S4 and Fig. 5, respectively). We rated the CoE as low for increased odds of SGA with prenatal cannabis use and downgraded the evidence for inconsistency and RoB (Table 2).

Secondary outcomes

We did not meta-analyze or assign a CoE rating for secondary outcomes, which included gestational age at birth (in weeks), LBW (< 2500 g), NICU admissions, and Apgar scores at 1 and 5 min. Across these secondary outcomes, unadjusted or adjusted associations or both were reported (Supplementary Tables S4 and S5). Gestational age at birth was reported in 27 studies with 8 reporting adjusted measures of association. Most studies showed that prenatal cannabis use significantly reduced gestational age at birth.
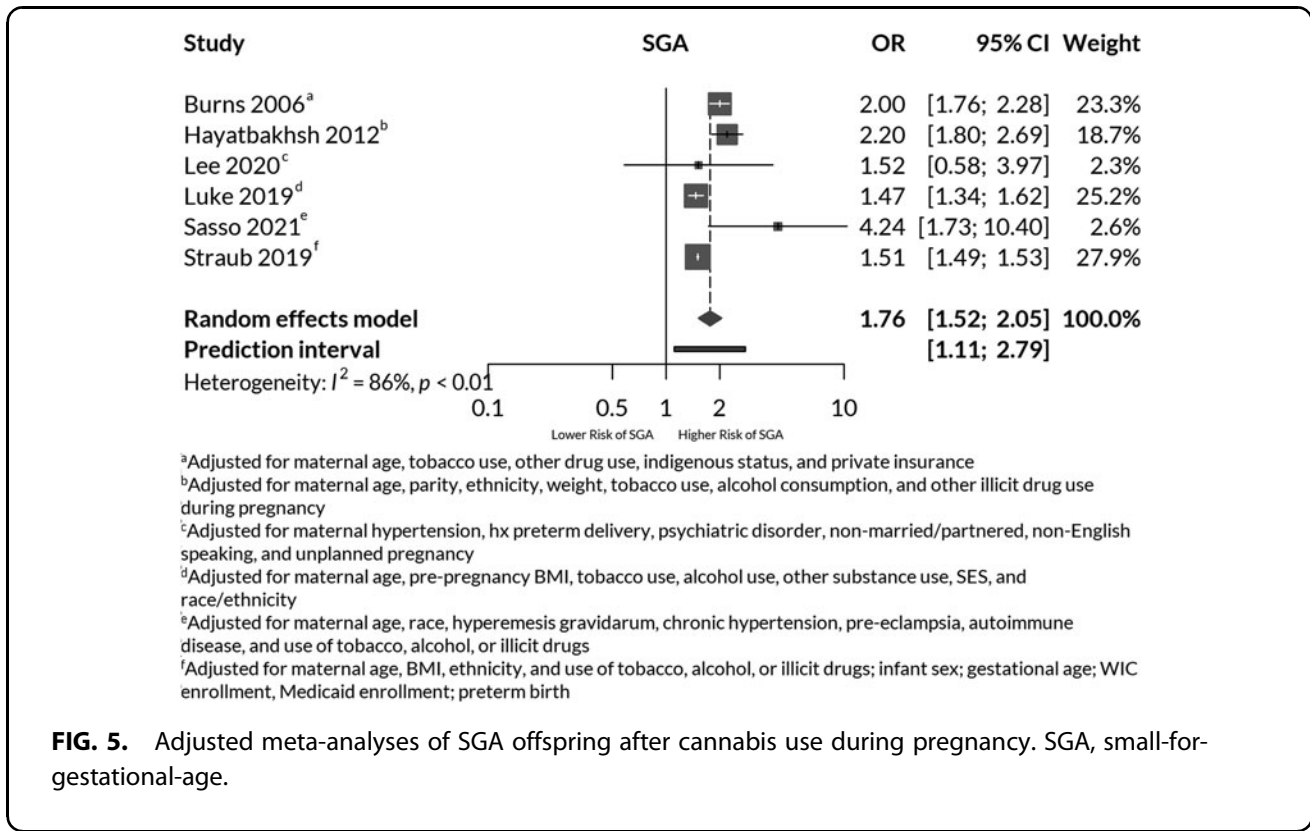
Our finding for this association is comparable to our meta-analysis result for PTB. Twenty-three studies

reported data on LBW with 19 studies reporting adjusted measures of association. A majority of the adjusted estimates were not significantly different between groups. This finding is also consistent in direction of association with our meta-analysis result of mean birthweight. NICU admissions were reported in 19 studies with 15 reporting adjusted measures of association. Most studies found prenatal cannabis use was associated with a significantly higher likelihood of NICU admissions (Supplementary Table S4).

Nine studies reported data on Apgar scores at 1 min with 5 studies reporting adjusted estimates, and 20 studies reported data at 5 min with 10 studies reporting adjusted estimates. Some studies reported Apgar scores as binary with cutoffs, while the majority reported means. The majority of studies found that Apgar scores at 1 and 5 min were not significantly different between groups (Supplementary Table S5).

Discussion

In this review, we found 53 studies evaluating prenatal cannabis use and relevant fetal and neonatal outcomes. Of our primary outcomes, after adjusting for confounding factors, we found low CoE that prenatal cannabis use remained an independent risk factor for PTB and SGA, and very low CoE for an increased likelihood of perinatal mortality. We found low CoE for no association with prenatal cannabis exposure and

FIG. 5. Adjusted meta-analyses of SGA offspring after cannabis use during pregnancy. SGA, small-for-gestational-age.

mean birthweight. Among secondary outcomes, we found that prenatal cannabis use was associated with decreased gestational age at birth, which is congruent with our observed association of prenatal cannabis use and PTB. Furthermore, we found that prenatal cannabis use was generally not significantly related to LBW, which was also consistent with our analysis of cannabis and mean birthweight. Finally, we observed that prenatal cannabis use was, in most studies, significantly associated with an increased likelihood of NICU admissions, but no consistent relationship was detected with Apgar scores.

It has been well demonstrated that PTB and SGA are strongly associated with increased offspring morbidity and mortality.[40] PTB is relatively common and affects 1 in 10 infants born in the United States.[41] SGA infants are five times more likely to die in the neonatal period and first years of life.[42] Thus, it is important to address modifiable risk factors for PTB and SGA, such as cannabis use, during the preconception or pregnancy period, which might help prevent these complications.

Compared with prior reviews focused on prenatal cannabis use, our review offers important strengths. Our review is current and comprehensive; many studies focused on examining cannabis use in pregnancy

have emerged since the most recently published large systematic reviews.[24,43,44] Also, similar to Conner et al,[24] our review used adjusted effect sizes in our meta-analyses accounting for confounders that were not addressed in other recent large reviews.[40,41] Our review also assessed many clinically relevant prenatal and neonatal outcomes similar to three recent reviews,[23,24,43] including perinatal mortality, which was not evaluated in the most recently published review.[23]

Marchand et al reviewed the associations of prenatal cannabis use on neonatal outcomes through August 2021.[23] Among 16 studies, they found significant increases in 7 adverse neonatal outcomes among women who used cannabis during pregnancy, including LBW, SGA, PTB, NICU admission, decreased mean birthweight, Apgar score at 1 min, and infant head circumference.[23] However, the authors did not adjust for confounding factors in their meta-analyses (e.g., tobacco, alcohol use), which might lead to biased associations, particularly with observational data. Although our review did not meta-analyze NICU admissions, in comparison we included more studies in our analysis; excluded for polysubstance use, including tobacco and alcohol; and did not find an association between prenatal cannabis exposure and birthweight.

Conner et al searched through August 2015, and similar to us, their pooled unadjusted data demonstrated an association between prenatal cannabis use and increased risk of PTB and LBW that, unlike our review, was no longer statistically significant after adjusting for tobacco use and other confounding factors.[24] While our review also did not show a difference in mean birthweight, we did demonstrate a greater risk of SGA with prenatal cannabis use. Their review also found that prenatal cannabis use is not an independent risk factor for adverse neonatal outcomes.

Gunn et al reviewed the associations of prenatal cannabis use on fetal outcomes through April 2014 and found that infants exposed to cannabis *in utero* had a higher risk of LBW and NICU admission.[43] Because the authors did not account for tobacco and alcohol use, the results were likely confounded. In contrast, our review did not meta-analyze NICU admissions, but most included studies found an association between *in utero* cannabis exposure and increased NICU admissions while adjusting for confounders.

Our review was based on an extensive literature search, but we had strict exclusion criteria to improve the quality of eligible studies, which likely reduced the number of included studies. Additionally, the existing literature for our review was limited by observational study designs and most studies included in our review determined cannabis use by participant self-report, which can underestimate the prevalence of cannabis use in pregnancy.[44,45]

Pregnant individuals also underreport their cannabis use by up to 60–70% of their actual use and there is no biological validation for self-reported dosing.[11,46,47] Even when use is reported accurately, it is hard to quantify and compare reported usage due to the lack of standardized dosing and routes of cannabis administration. Toxicological testing is preferred in lieu of, or in conjunction with, self-report. While more accurate than self-report, toxicology screening can also be limited by cross-reactivity with other substances, lack of sensitivity to detect intermittent use, overestimation of ongoing use, and an inability to determine timing and quantity of use.

Also, given the heterogeneity of the literature and limited overlapping measures between studies assessed, we were unable to ascertain the association of timing, frequency, quantity, concentration, or duration of prenatal cannabis use on fetal and neonatal outcomes. In addition, a majority of the included studies did not differentiate the mode of cannabis administration.

Because smoked cannabis is the most common form of use in pregnancy,[48] it is possible that our observed detrimental associations of cannabis on neonatal outcomes could be, in part, explained by the adverse prenatal effects of smoke inhalation. Comparative studies of different modes of cannabis administration are needed to better understand the effect of cannabis on pregnancy and neonatal outcomes.

Existing studies have also described an adverse association on offspring neurological development from maternal cannabis use in pregnancy, including an increased incidence of autism spectrum disorder.[43,46,49] Although our review included neonatal outcomes, we excluded studies that reported long-term offspring neurodevelopmental outcomes after prenatal cannabis exposure.

Conclusions and Implications

The results of our systematic review and meta-analysis suggest that prenatal cannabis exposure was independently associated with an increased risk for PTB, SGA, and perinatal mortality. However, our confidence in these findings was very low or low meaning that additional studies could meaningfully change our conclusions. Future research in this area should focus on the timing, frequency, route of administration, and potency of cannabis use, which is not well addressed in the existing literature.

Additionally, it is important for studies seeking to determine the association of cannabis use in pregnancy to ascertain cannabis use through screening methods with greater accuracy than participant self-report alone, and to adjust for important confounding factors, such as polysubstance, tobacco or alcohol use, or to use propensity scores or matching techniques to reduce selection biases. As prenatal cannabis use is becoming more common and cannabis potency is increasing, health care providers should discuss the uncertainty regarding the potential benefits and harms of cannabis use during pregnancy with individuals who are pregnant or trying to conceive.

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Authors' Contributions

J.O.L.: Conceptualization, methodology, investigation, data curation, writing–original draft, and visualization.

B.S.: Investigation, formal analysis, data curation, writing–review and editing, and visualization. S.R.: Investigation, formal analysis, data curation, writing–review and editing, and visualization. C.K.A.: Investigation, formal analysis, data curation, writing–review and editing, visualization, and project administration. S.D.: Investigation, formal analysis, data curation, writing–review and editing, and visualization. A.O.: Investigation, data curation. D.K.: Conceptualization, methodology, writing–review and editing, and funding acquisition. C.S.H.: Conceptualization, methodology, investigation, data curation, writing–original draft, visualization, formal analysis, and supervision.

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Supplementary Material
Supplementary Data
Supplementary Table S1
Supplementary Table S2
Supplementary Table S3
Supplementary Table S4
Supplementary Table S5
Supplementary Figure S1
Supplementary Figure S2
Supplementary Figure S3
Supplementary Figure S4

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Abbreviations Used

aOR = adjusted odds ratio
APGAR = appearance, pulse, grimace, activity, respiration
CI = confidence interval
CoE = certainty of evidence
GA = gestational age
GRADE = Grading of Recommendations Assessment, Development, and Evaluation
LBW = low birthweight
MD = mean difference
MJ = marijuana
MOOSE = Meta-analysis of Observational Studies in Epidemiology
NICU = neonatal intensive care unit
NOS = Newcastle–Ottawa Scale
NR = not reported
OR = odds ratio
PTB = preterm birth
RCT = randomized controlled trial
RoB = risk of bias
SD = standard deviation
SGA = small-for-gestational-age