The Effects of Cannabis Use during Pregnancy on Low Birth Weight and Preterm Birth: A Systematic Review and Meta-analysis

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Abstract

Objective Our objective was to summarize the literature regarding the effects of cannabis use during pregnancy on low birth weight (LBW), preterm birth (PTB), and small for gestational age (SGA).

Study Design This is a systematic review and meta-analysis. A literature search was conducted in PubMed, Scopus, EBSCO, and Web of Science in May 2021 and updated in November 2021. Only studies that assessed the isolated use of cannabis during pregnancy, controlling for cigarette smoking, and other illicit drug use were included. Data were synthesized using a narrative summary and pooled adjusted estimates, and 95% confidence intervals (CIs) were calculated for each outcome. Data were analyzed using Stata 13.0 with METAN software package, using random effects. Statistical heterogeneity was assessed using Cochran's Q and Higgins I2 tests.

Results In total, 32 studies were included with data from approximately 5.5 million women with the LBW outcome and 23 million with the PTB and SGA outcomes. Pregnant women using cannabis are at increased risk for LBW (adjusted odds ratio [aOR] = 1.52; 95% CI = [1.18; 1.96]), PTB (aOR = 1.39; 95% CI = [1.28; 1.51]), and SGA (aOR = 1.47; 95% CI = [1.38; 1.58]). Studies that assessed the type of PTB and gestational age at birth indicate higher risks of spontaneous PTB and of early or very-early PTBs associated with cannabis use during pregnancy. The few studies that assessed the timing and frequency of consumption suggest a dose–response effect, with higher odds of negative outcomes among women who reported heavy use and with continued use during the second and third trimesters of gestation.

Conclusion There is an effect of cannabis irrespective of other illicit drugs and tobacco despite high heterogeneity and low quality of evidence. There is a need to discuss public policies regarding cannabis' regulation and how it influences its consumption. Future studies should focus on the effects of cannabis's type (medicinal or recreational), timing, and dosage during pregnancy on perinatal outcomes.

Keywords
- cannabis
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Key Points
- Cannabis use during pregnancy is increasing.
- Cannabis has an independent effect on PTB, LBW, and SGA.
- Future studies should focus on the timing of exposure during pregnancy, mode of use, and dosage.

Substance use during pregnancy is an important public health issue. Cannabis is the most used illegal drug in Europe.[1] In the United States, it is legalized for medicinal use in 30 states and for recreational use in 9 of them, as well as in Canada.[2,3] Cannabis is in fact one of the most frequently used substances during pregnancy.[4,5] The prevalence of self-reported cannabis use in pregnancy varies between 2 and 5%, but it is as high as 15 and 28% in young, urban, and socioeconomically disadvantaged women.[6] The high prevalence of cannabis consumption during pregnancy is linked to legalization trends, perception of its safety, and its use to relieve pregnancy-related symptoms such as nausea and vomiting.[6] However, both the Center for Disease Control and Prevention and the American College of Obstetricians and Gynecologists recommend against using cannabis when trying to conceive, during pregnancy, and while breastfeeding, as well as the screening for cannabis use during antenatal care.[6]

Considering that the active component of cannabis—delta-9-tetrahydrocannabinol (THC)—crosses the placenta, there is concern regarding the risk of adverse fetal outcomes, namely stillbirth, fetal growth restriction, and fetal neurodevelopment consequences.[6] Also, THC is thought to be correlated to many of the cannabis's adverse effects; therefore, the increase in the average content of THC in cannabis products and, consequently, the amplification of its potency are major concerns.[7]

The literature varies regarding perinatal effects of prenatal cannabis use, as some studies show an increased risk of stillbirth or miscarriage,[8,9] fetal growth restriction and decrease in birth weight,[10,11] or neonatal intensive care admissions,[10] while others do not find these associations.[12–15] For the outcomes of preterm delivery and low birth weight (LBW), two systematic reviews had contradictory findings. In 2016, Gunn et al demonstrated the effect of cannabis exposure in utero and LBW. However, it was not possible to ascertain if it was a cannabis-only effect or if it was related to other substances such as alcohol or cigarette smoking.[10] In the same year, Conner et al found that marijuana use in pregnancy was not a risk factor, neither for LBW nor for preterm delivery, after adjusting for confounding factors such as cigarette use.[16] Study design, sample size, exposure assessment, as well as measure of confounding risk factors, and maternal characteristics are among the reasons that may explain the inconsistencies.[2,10,16]

As the consumption of cannabis in pregnancy is increasing, but its consequences are still unclear, it is crucial to continue to evaluate the potential risks and effects of prenatal exposure on pregnant women and newborns to guide clinical practice and implement effective public health recommendations and policies on substance use during pregnancy. As preterm birth (PTB) and LBW are the main risk factors for infant mortality[17] and the outcomes of cannabis exposure on fetal growth are less certain, the aim of this review is to summarize the current literature regarding the effects of cannabis use during pregnancy on LBW, PTB and small for gestational age (SGA) in live births.

Materials and Methods

The Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) principles were followed to conduct this study.[18] The research question guiding this review was: What are the effects of cannabis use during pregnancy on the rates of LBW, PTB, and SGA in live births? The protocol for this review was registered in PROSPERO (registration number: CRD42021252433).

Search Strategy

A literature search was conducted by the first author (I.B.) using four electronic databases: PubMed, Scopus, EBSCO, and Web of Science, in May 2021, and updated in November 2021, to identify all the relevant studies addressing the effects of cannabis use during pregnancy on the prevalence of LBW, PTB, and SGA in live births. These outcomes were classified according to the World Health Organization definitions: LBW as weight at birth of <2,500 g,[19] PTB as any birth before 37 completed weeks of gestation or fewer than 259 days since the first day of the woman's last menstrual period,[20] and SGA as smaller in size than normal for their gestational age, commonly defined as a weight below the 10th percentile for the gestational age.[21] One study[8] included in this review defined LBW as <2,400 g for female infants.

No language restriction was applied. The search was restricted to studies published after 2000 because of the increase in THC potency in the last decades.[22] The mesh terms "marijuana use", "marijuana abuse", "cannabis," and "cannabinoids" were used to define the search expression, being adapted according to the different datasets. The search was followed by reference tracking, examining the references of the selected publications based on full-text assessment.

Study Selection

The inclusion criteria were defined as original, empirical, peer-reviewed full-length studies published after January 1, 2000, in Portuguese, English, Spanish, or French that assessed the isolated use of cannabis during pregnancy and the outcomes LBW, PTB, and SGA compared to a control group that did not use cannabis or other illicit drugs during pregnancy. Considering the association between cannabis use and the

use of other illicit drugs and cigarette smoking, only studies reporting results controlled for cigarette smoking and other illicit drugs (by study design or analysis) were included in the current analysis, to avoid confounding.[8,23]

The exclusion criteria included studies not addressing the research question; studies of populations that were nonrepresentative of the general population of pregnant women (e.g., substance use disorders and medical comorbidities); studies for which it was not possible to extract data for cannabis users separately from others substance users; studies that did not control the estimates for confounders, at least for tobacco and other illicit drugs; as well as nonoriginal full-length studies (reviews, meta-analyses, comments, editorials, notes, newspapers articles, conference proceedings, reports, and guidelines).

Quality Assessment

Rather than using quality scoring systems, the criteria used in a previous review[16] that assessed study quality based on six factors considered most likely to threaten study validity when evaluating the effect of drug use on birth weight and gestational age were employed:

- Whether cannabis use was defined by objective measures (e.g., urine or hair drug tests).
- Whether quantity of cannabis use was addressed.
- If other drug use was excluded from the study or adjusted for in the analysis.
- Whether the results were adjusted for tobacco exposure.
- Selection bias (convenience samples; significant or selective losses to follow-up).
- Inclusion of multiple gestations and/or anomalies.

In this review, we adapted item 1 by including hospital admission for "substance use disorder-cannabis" (International Classification of Diseases, 10th Revision (ICD-10): F12.0–F12.9 = cannabis-related disorders, T40.7 = poisoning by cannabis) or "cannabis dependence or abuse" (ICD-9: 304.3 = cannabis dependence, 305.2 = nondependent cannabis abuse) as an objective criterion, as they rely on a clinical diagnosis. We also included frequency in item 2, as some studies reported this metric. Studies were classified as high quality if complying with three or more criteria.

Data Extraction

The review followed a two-phased screening process. First, titles were screened, and then, abstracts were assessed to determine whether they met the inclusion criteria. Second, papers that met the criteria and papers with insufficient information on the abstract were retrieved and reviewed for full-text screening. Two reviewers (I.B. and R.M.S.M.D.) took part in this process. Any disagreement related to the inclusion criteria was resolved based on consensus. The PRISMA flow diagram was used to visualize the study selection process.[18]

Data extracted included general information (authors, year of publication, and country); study characteristics (sample size, year of research, study design, and context); method for assessing cannabis use (self-report and/or objective measure); frequency or quantity of cannabis consumption; type of cannabis use (recreational or medical); and outcome data/results (prevalence of cannabis use during pregnancy, rates of LBW, PTB and SGA in exposed and unexposed groups, adjusted estimates of cannabis use during pregnancy on LBW, PTB and SGA, and confounders).

Data Synthesis

Data were synthesized using a narrative summary. Pooled adjusted estimates and 95% confidence intervals (CI) were calculated for each of the outcomes if two or more studies reported the same outcome. We pooled the adjusted estimates informed in the original studies. The confounders adjusted for in each study varied, but all studies controlled for tobacco, alcohol, and illicit drugs. We planned to conduct subgroup analysis for study quality, amount of cannabis used, and type of use (medical or recreational). As few studies reported quantity, we used the classification of cannabis dependence or abuse or substance use disorder associated with cannabis as a proxy for intensive use. Only one study reported medical use, and the only pregnant woman with medical use was excluded.[24] Therefore, we were not able to conduct this subgroup analyses. Data were analyzed using Stata 13.0 with METAN software package, using random effects. Statistical heterogeneity was assessed using Cochran's Q and Higgins I2 tests. In order to analyze the quality of evidence for each outcome included in the meta-analysis, we used the Grading of Recommendations Assessment, Development, and Evaluation (GRADE).[25]

Results

From the 2,574 papers initially identified through database searching, 737 were duplicates, 1,837 were screened for eligibility criteria, and 86 were assessed based on full-text (one paper had no full-text available). The main reasons for study's exclusion were (1) not evaluating the outcome of interest/not related to the research question ($n = 27$), (2) nonoriginal full-length studies ($n = 13$), (3) studies for which it was not possible to assess the effect of cannabis alone ($n = 7$), or (4) studies that did not present adjustment for confounders ($n = 8$). Six additional references were identified by reference tracking, with inclusion of one study, totaling a final sample of 32 studies. The screening process is summarized in ►Fig. 1.

Characteristics of the Studies

Among the 32 included studies, 26 were cohort studies (retrospective [$n = 17$], prospective [$n = 8$], prospective multicenter [$n = 1$]), 4 were cross-sectional, 1 was a case-control study, and 1 could not be classified.[14] More than half of the studies were from the United States ($n = 22$), four were from Australia, and three from Canada. Only two studies were from European countries: one from Czech Republic[26] and one from France.[27] The study presenting multicountry data included Australia, Ireland, New Zealand, and the United Kingdom.[28]

In the quality assessment, 22 studies were classified as high quality and 10 as low quality, mainly due to the lack of

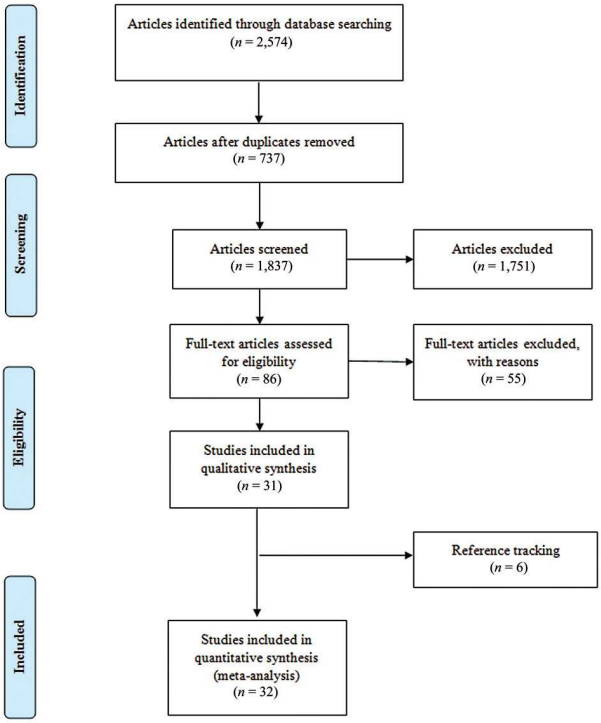

Fig. 1 Flow chart of included studies.

an objective measure to assess cannabis use during pregnancy, no report of quantity or frequency of use, and risk of selection bias. ►**Table 1** presents a summary description of the characteristics of the studies.

Cannabis Assessment

Most studies did not present information regarding the type of cannabis use (medical or recreational use). Only three studies clearly stated that cannabis use was recreational.[24,29,30] The great majority of studies relied only on maternal self-report ($n = 14$). The timing of self-report measurement varied between studies: during antenatal appointments[8,15,16,24,31–37]; at delivery[13,15,27,38–40]; or after delivery by telephone interview.[14,41–43] Some studies also included exposure to cannabis before pregnancy.[14,24,42] Eleven studies used maternal urine, hair, or meconium test screening, nine of them assessing cannabis exposure only once, either during pregnancy[8,15,16,29,30,44] or at the time of delivery.[13,38,45] Only two studies used objective measures at various time points, both showing a reduction in the prevalence of cannabis use throughout pregnancy.[34,36] Seven studies used ICD diagnosis (ICD-9 [$n = 2$], ICD-10 [$n = 4$], and ICD-9 and ICD-10 [$n = 1$]) as a measure of abuse, addiction, or mental or behavioral disorder associated with cannabis use during pregnancy,[26,46–48] childbirth[46–50] or in the period from the 12 months before pregnancy to delivery.[51]

The prevalence of cannabis use during pregnancy ranged from 0.005[26] to 39%.[31] Six studies[24,29,35,46,49,50] evaluated the trend of use. Five identified an increase in the prevalence of cannabis use during pregnancy,[24,35,46,49,50] while Straub et al[29] did not identify any difference in prevalence rates in the pre- and postlegalization periods of recreational use of cannabis.

Outcomes

Regarding the outcomes of interest, 19 studies evaluated LBW, 27 assessed PTB, and 21 presented data for SGA. Based on the pooled adjusted analysis, pregnant women who use cannabis during pregnancy are at increased risk for LBW (odds ratio [OR] = 1.52; 95%CI = 1.18; 1.96; ►**Fig. 2**), PTB (OR = 1.39; 95%CI = 1.28; 1.51; ►**Fig. 3**), and SGA (OR = 1.47; 95%CI: 1.38; 1.58; ►**Fig. 4**). High levels of heterogeneity were observed for the three outcomes: $I^2 = 93.3\%$, $p < 0.001$ for LBW; $I^2 = 90.7\%$, $p < 0.001$ for PTB; and $I^2 = 91.7\%$, $p < 0.001$ for SGA. The planned subgroup analysis could not explain the observed heterogeneity (►**Figs. 2–4**).

►**Table 2** shows the quality of evidence according to the GRADE system. For the three outcomes (LBW, PTB, and SGA), the quality of evidence was very low, due to the observational design of the studies, high heterogeneity, and risk of bias due to measurement errors and potential residual confounding.

Specific Aspects Regarding Preterm Birth

Five studies assessed the gestational age in weeks stratifying PTB into different categories,[27,28,32,39,46] and five studies[27,28,34,35,40] indicated the type of preterm delivery (spontaneous or provider initiated). The studies that stratified PTB by weeks of gestation found a higher risk of early PTB (<34 weeks of gestation)[39] and of very PTB (<32 weeks of gestation)[27,28,32,46] in cannabis users. The five studies[27,28,34,35,40] that assessed the type of preterm delivery identified a higher risk of spontaneous preterm birth (SPTB) in cannabis users, irrespective of cigarette smoking.[28,40] In one study,[40] simultaneous marijuana use and cigarette smoking were associated with higher risk of SPTB (RR = 1.64, 95%CI = 1.23; 2.18), but no higher risk associated with provider-initiated PTB was observed. In a national survey in France, Saurel-Cubizolles et al[27] identified a significantly higher rate of SPTB (6.4 vs. 2.8%) but not of provider-initiated PTB in cannabis users.

Timing and Frequency of Cannabis Use and Interaction with Cigarette Smoking

Seven studies assessed timing or frequency of cannabis use and six reported outcomes according to the level of exposure. Two studies[28,40] reported higher prevalence of PTB in women who used cannabis during the second and third gestational trimesters when compared to those who only used during the first trimester. Two studies identified significantly higher prevalence of LBW[42,43] and SGA[43] in women who reported high frequency of cannabis consumption (at least once a week), both in smoking and in nonsmoking women, and one study[27] reported a dose response effect for PTB (5.3, 9.9, and 12.3% in nonusers, in those who used less than once a month, and among more frequent users, respectively).

Nine studies evaluated the interaction between cannabis and tobacco use, six of those[13,27,28,34,37,40] did not find statistical evidence of an additive interaction between cannabis and tobacco for the studied outcomes. Corsi et al[32]

Table 1 Description of studies

Study, year of publication, and country	Study design; year of research; sample size	Context	Assessment of cannabis exposure	Outcomes	Confounders adjustment	Prevalence of cannabis use	Overall quality assessment
Alhusen et al,[31] 2013, the United States	Prospective cohort; 2009–2010; 166 (64 users, 102 nonusers)	Three obstetric clinics	Self-report at antenatal visits between 24 and 28 wk of gestation	LBW; PTB; SGA	Unclear. Adjusted for tobacco	39%	Low
Bada et al,[38] 2005, the United States	Prospective cohort; 1993–1995; 8,637	Four university hospitals	Self-report at delivery; meconium analysis	LBW; PTB; SGA	Medical and obstetric complications, hospitalization during pregnancy, maternal weight gain during pregnancy, PNC, maternal age, Medicaid insurance, infant's gender, and race, clinical site, and legal and illegal drug use	9.4%	Low
Bailey et al,[45] 2020, the United States	Two prospective cohorts; not informed; 1,062	Appalachian cohort: all births in the health system of five delivery hospitals in two states in South Central Appalachia; Rocky Mountain cohort: all births in the health system of six delivery hospitals in one state in the Western US.	Urine analysis at birth	LBW; PTB	Maternal age, marital status, race, parity, medical insurance, tobacco, alcohol, benzodiazepines and opioids, delivery year	NI	High
Bandoli et al,[46] 2021, the United States	Retrospective cohort; 2011–2017; 3,067,069	Administrative birth cohort of single deliveries in California	ICD-9 and ICD-10 during pregnancy or delivery	PTB; SGA	Stratified for tobacco use. Adjusted for maternal race and ethnicity, age, payer source, education, prepregnancy BMI, preexisting hypertension and diabetes, alcohol-related diagnosis and mental health disorders.	1.0%	High
Bonello et al,[51] 2014, Australia	Retrospective cohort; 2003–2006; 367 cannabis users, 13,113 nonusers	Population linked data (baby birth records from NSW Midwife Data Collection of primiparous women and maternal hospital records from the NSW Admitted Patients Data Collection)	Hospital admission with a diagnosis of mental and behavioral disorders due to use of cannabinoids (ICD-10-AM F12) in the period from the 12th mo before pregnancy to the end of pregnancy.	LBW; PTB	Maternal age, preexisting maternal diabetes and hypertension, pregnancy complications, smoking, remoteness of living area, Index of Relative Socio-economic Disadvantage, maternal country of birth, delivery method, infant gender and fetal/neonatal death	NI	High
Burns et al, [47] 2006, Australia	Cross-sectional; 1998–2002; 416,834 live births, 2,172 cannabis users	Population linked data (NSW Inpatient Statistics Collection and Birth Records from the NSW Midwives Data Collection)	Hospital admission during pregnancy or delivery with mental or behavioral disorder or poisoning by cannabis (ICD-10AM codes[a])	PTB; SGA	Maternal age, smoking, other drug use (stimulants, opioids, and alcohol), indigenous status, private insurance.	0.52%	High

(*Continued*)

Table 1 (*Continued*)

Study, year of publication, and country	Study design; year of research; sample size	Context	Assessment of cannabis exposure	Outcomes	Confounders adjustment	Prevalence of cannabis use	Overall quality assessment
Chabarria et al,[39] 2016, the United States	Retrospective cohort, 2011–2015; 12,069	Referral hospitals associated with Baylor College of Medicine	Self-report at delivery	PTB; SGA	Stratified for tobacco use and adjusted for age, race, marital status, parity, chronic hypertension, and pregestational and gestational diabetes.	0.88%	Low
Coleman-Cowger et al[8], 2018, the United States	Prospective cohort, 2017; 500 women; 338 newborns	Two urban university obstetric clinics	Self-report + urine and hair testing during one antenatal care visit	LBW; PTB	Stratified for tobacco use. LBW Adjusted for gestational age. PTB adjusted for maternal age and gravidity.	12.1% (10.7% in women who delivered)	Low
Conner et al,[16] 2015, the United States	Retrospective cohort; 2004–2008; 8,138	Washington University in St. Louis Medical Center	Self-report or positive urine at least once during pregnancy	LBW	Smoking, other drug use and African American race.	8.4%	High
Corsi et al,[32] 2019, Canada	Retrospective cohort; 2012–2017; 661,617	Ontario's Better Outcomes Registry and Network (BORN) (all births in the province, 40% of births in Canada)	Self-report at first visit to routine antenatal care	PTB; SGA	Parity; antenatal care by family physician, obstetrician, or midwife; year of birth; tobacco smoking; alcohol use; use of selective serotonin reuptake inhibitors; opioid use; use of other drugs; maternal mental health conditions.	1.4%	High
Crume et al,[41] 2018, the United States	Cross-sectional, 2014–2015; 3,207	Colorado Pregnancy Risk Assessment Monitoring System; linkage with birth certificates for additional maternal demographic, health information, and neonatal outcomes	Self-report 2–4 mo after postpartum	LBW; PTB; SGA	Maternal age, race/ethnicity, level of education and tobacco use.	Total: 5.7%; In the first trimester: 4.8%; In the third trimester: 2.4%	Low
Haight et al,[42] 2021, the United States	Cross-sectional; 2017; 5,548	Pregnancy Risk Assessment Monitoring System (PRAMS) from eight U.S. states (Alaska, Illinois, Maine, New Mexico, New York, North Dakota, Pennsylvania, and West Virginia), linkage with birth certificates for birth outcomes	Self-report 2–6 mo after delivery	LBW; PTB; SGA	Maternal age, race or ethnicity, marital status, education, prepregnancy BMI, insurance, parity, and month of entry into prenatal care. Models included an interaction term between cannabis use and cigarette smoking status. Results stratified by cigarette smoking status.	4.2% (1.7% for low frequency use; 2.6% for high-frequency use)	Low

Table 1 (*Continued*)

Study, year of publication, and country	Study design; year of research; sample size	Context	Assessment of cannabis exposure	Outcomes	Confounders adjustment	Prevalence of cannabis use	Overall quality assessment
Hayatbakhsh et al,[33] 2012, Australia	Prospective cohort; 2000–2006; 24,874	Tertiary maternity hospital	Self-report at the first antenatal visit	LBW; PTB; SGA	Maternal age, parity, ethnicity, weight, cigarette smoking, alcohol consumption, and use of other illicit drugs during pregnancy.	2.6%	High
Kharbanda et al,[44] 2020, the United States	Retrospective cohort; 2015–2017; 3,435	Administrative and electronic health record in a large integrated health system.	Urine toxicology screen at first antenatal care visit	LBW; PTB; SGA	Smoking during pregnancy, age, prepregnancy BMI, and race/ethnicity. Analysis stratified by maternal smoking.	8.2%	High
Klebanoff et al,[34] 2020, the United States	Prospective cohort; 2010–2015; 363	The Ohio Perinatal Research Network Perinatal Research Repository (PRR) at the Ohio State University.	Self-report at enrollment during first or second trimester of pregnancy+ record abstraction at delivery+ urine toxicology at enrollment and approximately once in each subsequent trimester	PTB	Marital status, race, tobacco, education, homeless, physical abuse, planned pregnancy, alcohol use, opiate, cocaine, parity, maternal age, maternal height, maternal prepregnancy weight, perceived stress, depressive symptoms, trait anxiety, sleep quality and perceived everyday discrimination. Year of entry in the study and mean gestational age at entry.	33%	Low
Leemaqz et al,[28] 2016, Multicountry (Australia, Ireland, New Zealand, the United Kingdom)	Multicenter prospective cohort; 2004–2011; 5,588	Multicenter Screening for Pregnancy Endpoints (SCOPE) study.	Self-report at 15 and 20 wk of gestation	Spontaneous PTB; SGA	Stratified for tobacco use. Adjusted for maternal age, BMI, SEI, smoking. Interaction term for smoking and cannabis use.	5.6% (3.7% in the United Kingdom to 11.6% in Australia)	High
Luke et al,[35] 2018, Canada	Retrospective cohort; 2008–2016; 243,140	Perinatal data registry of perinatal services in British Columbia (covers 99% of births in British Columbia)	Self-report at the first antenatal care visit	Spontaneous PTB; SGA	Maternal age, prepregnancy BMI, tobacco use, alcohol use, other drugs use, socioeconomic status, and race/ethnicity.	2.4%	High
Mark et al,[36] 2015, the United States	Retrospective cohort; 2009–2010; 396 women, 170 birth outcomes	University-affiliated prenatal clinic	Self-report or urine toxicology testing at the first obstetrical visit and urine toxicology at delivery	LBW	Maternal age, race, education, cigarette smoking, marital status, employment, history of abuse.	Initial visit: 29.3%; At delivery: 1.9%	Low
Michalski et al,[24] 2020, Canada	Prospective cohort; 2013–2019; 2,229 women, 1,778 birth outcomes	Ontario Birth Study at the Mount Sinai Hospital, Toronto	Self-report between 12 and 16 wk of gestation	LBW; PTB; SGA	PTB and SGA adjusted for maternal age, year, BMI, household income, education, ethnicity, alcohol use, tobacco use, anxiety or depression symptoms, prescription antidepressant use, prescription pain medication use, infant sex. LBW also adjusted for GA.	9.7%	High

(*Continued*)

Table 1 (*Continued*)

Study, year of publication, and country	Study design; year of research; sample size	Context	Assessment of cannabis exposure	Outcomes	Confounders adjustment	Prevalence of cannabis use	Overall quality assessment
Mravčík et al,[26] 2020. Czech Republic	Prospective cohort; 2000–2014; users 69, nonusers 1,511,310	Database-linked study (National Registry of Reproductive Health and National Register of in-Patient Treatment)	Substance abuse disorder (ICD-10) at hospital admission during pregnancy	SGA in term births	Marital age, marital status, education, concurrent smoking and substance use, prenatal care.	0.005%	High
Nawa et al,[40] 2020, the United States	Case-control; 1998–2018; 8,261	Boston Birth Cohort (cases= preterm and low birth weight mother–infant pairs; controls = term mother–infant pairs)	Self-report within a few days postpartum	PTB (total, spontaneous; induced)	Maternal age, race/ethnicity, marital status, parity, education, income, alcohol use during pregnancy, tobacco smoking during pregnancy and year of child's birth.	Preterm: 5.2%; Term: 3.5%	High
Nguyen and Harley,[43] 2021, the United States	Retrospective cohort; 2017–2019; 32,583	Pregnancy Risk Assessment Monitoring System in 20 U.S. States (legal recreational and medical use in four states, only legal medical use in 12)	Self-report 2–4 mo postpartum	LBW; PTB; SGA	Maternal age, race, education, parity, marital status, tobacco, any prenatal care use, health insurance, state of residency, year of interview.	4.9% (0.9%—light users, 0.6%—moderate users, 2.5% heavy users)	Low
Oni et al,[48] 2021, Australia	Retrospective cohort; 2007–2016; 622,640	Three New South Wales linked datasets (NSW Perinatal Data Collection; NSW Admitted Patient Data Collection; Cause of Death Unit Record File) and the Socio-Economic Indexes for Areas (SEIFA)	At least one hospital admission during pregnancy or delivery with cannabis-related ICD-10-AM diagnostic code	LBW; PTB	Multilevel logistic regression. Maternal age, smoking, substance use disorders (opioids, stimulants, alcohol, multidrug), Indigenous status, Medicare health insurance, antenatal care attendance, plurality of birth and SEIFA: IRSAD score; maternal comorbidities (preeclampsia, chronic/preexisting and gestational hypertension, chronic/preexisting diabetes and gestational diabetes.	0.3%	High
Petrangelo et al,[49] 2018, the United States	Retrospective cohort; 1999–2013; 12,578,557	National Inpatient sample (includes 44 U.S. states representing over 20% of the admissions to community hospitals nationwide)	Cannabis dependence or abuse (ICD-9) registered at birth	PTB; SGA	Maternal age, race, hospital location, type of insurance, income, multiple births, hypertension, preexisting diabetes mellitus, smoking, alcohol use, other illicit drug use	0.53%	High
Sasso et al,[30] 2021, the United States	Retrospective cohort; 2015–2018;	Safety Net Hospital in Southern California	Self-report or urine toxicology during any trimester of pregnancy	PTB; SGA	Maternal age, race, preeclampsia, autoimmune disease, hyperemesis gravidarum, and chronic hypertension and tobacco.	5.4%	Low

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Table 1 (*Continued*)

Study, year of publication, and country	Study design; year of research; sample size	Context	Assessment of cannabis exposure	Outcomes	Confounders adjustment	Prevalence of cannabis use	Overall quality assessment
Saurel-Cubizolles et al,[27] 2014, France	Cross-sectional; 2010; 13,545	All public and private French maternity units	Self-report 2–3 d after delivery at the postpartum ward	PTB (total, spontaneous, induced); SGA	Maternal age, parity, nationality, cohabiting, level of education, employment status, income of the household, BMI, alcohol consumption, smoking in the third trimester	1.2%	High
Schempf and Strobino, [13], 2008, the United States	Retrospective cohort; 1995–1996; 808	Johns Hopkins Hospital	Self-report, medical records, or drug screen postpartum	LBW	Other drug use, including tobacco and alcohol.	11%	High
Shi et al,[50] 2021, the United States	Retrospective cohort; 2001–2012 (except year 2006); 4,830,239	Data-based linked study (hospital discharge records and infants' birth and death certificates. Includes all live births delivered in California hospitals in the period)	Cannabis dependence or abuse registered at birth (ICD-9)	LBW; PTB; SGA	Maternal age, educational attainment, race and ethnicity, health insurance, delivery mode, birth history, hypertension, diabetes, thyroid disease, anemia, cardiovascular disease, pain, major depressive disorder, anxiety disorder, and other mental disorders, adequate prenatal care, tobacco use, alcohol use disorder, opioid and other drug use disorders, fathers' educational attainment, Infant sex, health insurance, and birth year.	0.42%	High
Straub et al,[29] 2021, the United States	Retrospective cohort; 2011–2016; 5,343	Health record data from two obstetric hospitals	Urine drug screen during pregnancy	LBW; SGA	Maternal age, BMI at delivery, illicit screen positive, tobacco use, alcohol use, adequate prenatal care, WIC enrollment, Medicaid, parity, ethnicity, gestational diabetes, baby sex, PTB	23.7%	High
Van Gelder et al,[14] 2010, the United States	NI (Analysis of controls from a case-control study); 1997–2004; 5,871 women, 5,661 infants	Controls of the National Birth Defects Prevention Study in 10 U.S. states	Self-report collected 6 wk to 24 mo after due date. Information on type, timing, and frequency of drug use from 3 mo before pregnancy until birth	LBW; PTB	LBW: adjusted for gestational age and cigarette smoking; PTB: adjusted for cigarette smoking, binge drinking and gestational weight gain.	3.2%	High

(*Continued*)

Table 1 (*Continued*)

Study, year of publication, and country	Study design; year of research; sample size	Context	Assessment of cannabis exposure	Outcomes	Confounders adjustment	Prevalence of cannabis use	Overall quality assessment
Warshak et al,[15] 2015, the United States	Retrospective cohort; 2008–2011; 6,468	University of Cincinnati Medical Center	Self-report, drug screen, or medical register during antenatal care or at delivery	PTB; SGA	Maternal age, race, parity, BMI and no prenatal care among nonsmoking women.	5.6%	High
Washio et al,[37] 2018, the United States	Retrospective cohort; 2014–2015; 11,020	Christiana Care Health System (cares for 70% of state residents)	Self-report at the first antenatal care visit	LBW; PTB	Maternal age, race, medicaid status, parity, gravida, prepregnancy BMI, gestational diabetes, high-risk hypertension, pregnancy-induced hypertension, cigarette smoking, alcohol, use, other illicit drugs	3.0%	High

Abbreviations: BMI, body mass index; GA, gestational age; ICD, International Classification of Diseases; LBW, low birth weight; NI, no information; NSW, New South Wales; PNC, postnatal care; PTB, preterm birth; SEI, socioeconomic index; SEIFA/IRSAD score, Socio-Economic Indexes for Areas/Index of Relative Socio-Economic Advantage and Disadvantage; SGA, small for gestational age; WIC, women, infant and children program.

[a]ICD-10AM codes are an Australian modification to the World Health Organization ICD-10 classification of diseases and health related problems (National centre for Classification in National Centre for Classification in Health 1998).

reported a positive interaction term for risk difference. Chabarria et al[39] identified increased adjusted odds ratio above cigarette smoking alone for PTB, suggestive of a summative, additive, or potentially synergistic effect of marijuana with concurrent cigarette smoking. Nguyen et al[43] identified increased odds for concomitant use of cannabis and tobacco, greater than the use of each drug alone, with an apparent additive interaction for SGA but the authors did not test for interaction.

Discussion

The results of this review, with the inclusion of approximately 5.5 million women with the LBW outcome and 23 million with the PTB and SGA outcomes, showed a 52% increase in the occurrence of LBW, 47% increase in SGA, and a 39% increase in PTB associated with cannabis use during pregnancy. Regarding to previous systematic reviews/meta-analyses on the topic,[10,16] these results show an independent effect of cannabis despite the use of other illicit drugs and tobacco during pregnancy.

However, the quality of the evidence is very low due to the observational design of the studies, the high heterogeneity, and the possible risk of bias, mainly due to measuring errors of the cannabis exposure and the possibility of residual confounding. Most of the identified studies had a longitudinal design, but few evaluated the timing of exposure to cannabis throughout pregnancy and the frequency of use. Only two assessed the type of use (recreational or medicinal), and none assessed the amount and type of cannabis used. These methodological limitations are possibly among the sources of the high heterogeneity observed.

Some studies were carried out in contexts where cannabis is legal for medical use,[43,44] for medical or recreational use,[35,43] or in pre- and postlegalization contexts,[29] which may affect women's report. Thus, the assessment of cannabis use based on the self-report, used in most of the studies, may underestimate the prevalence of cannabis use during pregnancy, particularly in regions/countries where its use is not legal.

Unlike previous reviews, we identified studies in which exposure to cannabis was based on hospitalization during pregnancy or childbirth with ICD-9 or ICD-10 codes related to abuse, addiction, or mental or behavioral disorder associated with cannabis use, which was used as a proxy for heavy use. However, this can also misclassify consumers without a clinical diagnosis as nonconsumers, attenuating the observed estimates.

This meta-analysis pooled the adjusted estimates provided by the original studies. Most studies do not present a theoretical model for the analysis performed and adjust for a very different set of variables. Studies that used secondary data could only adjust for variables that were available, which, in general, are not collected in a standardized way, resulting in insufficient adjustments and the possibility of residual confounding. LBW, PTB, and SGA are multicausal outcomes and cannabis use is associated with several maternal characteristics and conditions that are risk factors for these negative

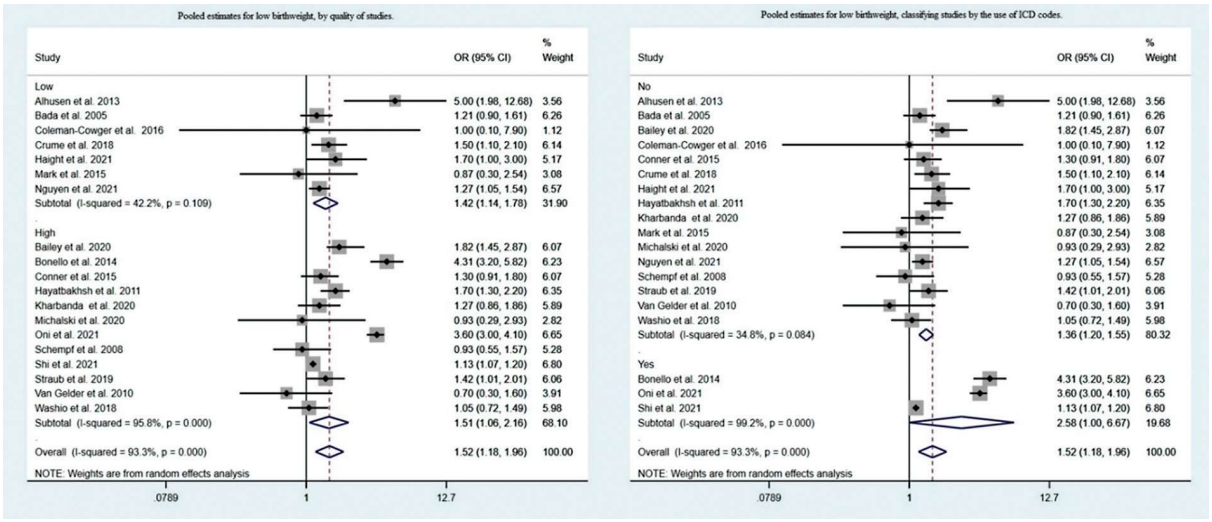

Fig. 2 Pooled estimates for low birth weight analysis. CI, confidence interval; ICD, International Classification of Disease; OR, odds ratio.

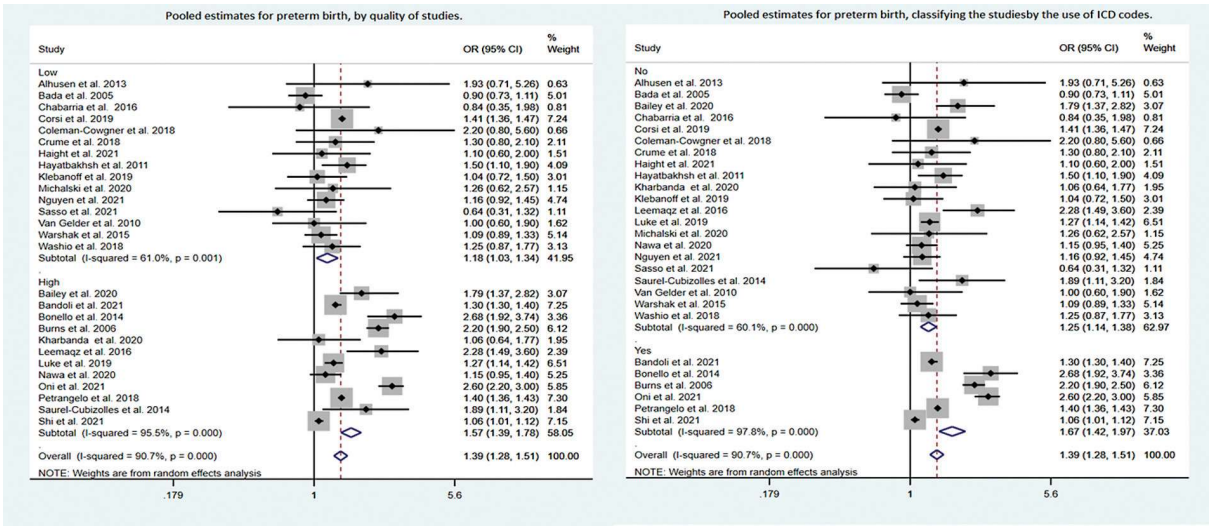

Fig. 3 Pooled estimates for preterm birth analysis. CI, confidence interval; ICD, International Classification of Disease; OR, odds ratio.

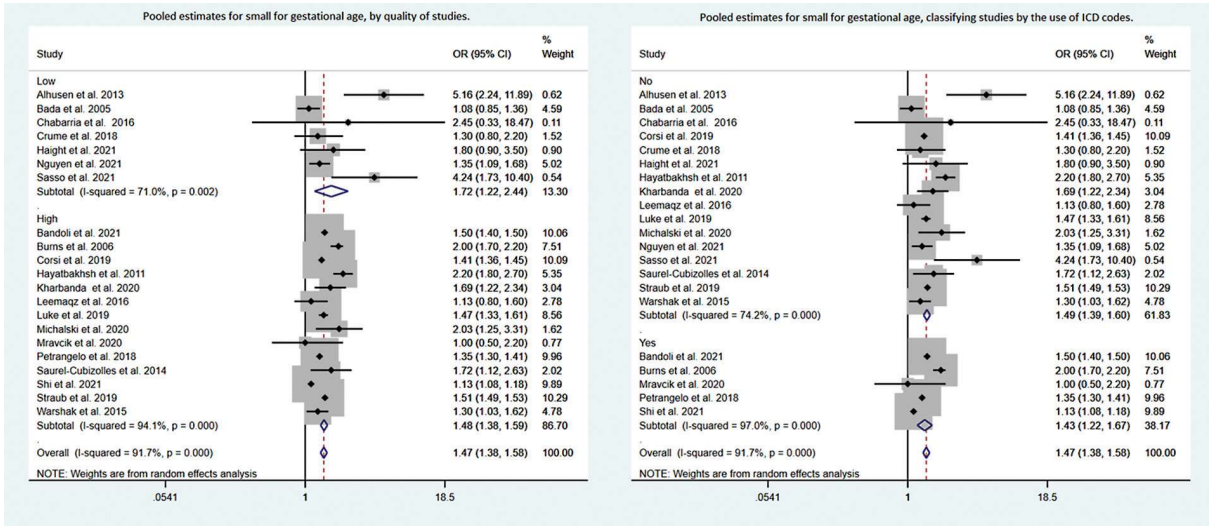

Fig. 4 Pooled estimates for SGA analysis. CI, confidence interval; ICD, International Classification of Disease; OR, odds ratio; SGA, small for gestational age.

Table 2 Summary of results for the quality of evidence according to GRADE guidelines

Outcome	Group effect (95% CI)	Participants (number of studies)	Quality of evidence (GRADE)
LBW	1.52 (1.18–1.96)	5,579,127 (19)	Very low[a]
PTB	1.39 (1.28–1.51)	22,578,522 (27)	Very low[a]
SGA	1.47 (1.38–1.58)	23,432,419 (21)	Very low[a]

Abbreviations: CI, confidence interval; GRADE, Grading of Recommendations Assessment, Development and Evaluation; LBW, low birth weight; PTB, preterm birth; SGA, small for gestational age.
[a]Observational studies with high heterogeneity and risk of bias due to measurement errors and potential residual confounding.

outcomes.[3] Therefore, differences in populations and the adjusted analysis may be important sources of heterogeneity.

The observed result of higher rates of PTB, LBW, and SGA in cannabis users has biological plausibility[22,52–55] and is consistent with other studies that demonstrated lower fetal weight gain and lower gestational age at birth in cannabis users.[56–61] Studies that assessed the type of PTB and gestational age at birth indicate higher risks of SPTB and of early or very-early PTBs associated with cannabis use during pregnancy. SPTBs are more frequently associated with maternal conditions, such as maternal age, prepregnancy weight status, micronutrient deficiencies, infectious diseases, tobacco use, poor mental health, and intimate partner violence.[62,63] The higher prevalence of SPTB in cannabis users reported in the studies included in this review, and apparently no higher risk for induced PTB, is consistent with these known maternal characteristics associated with PTB.

The higher odds of negative outcomes among women who reported heavy use and with continued use during the second and third trimesters of gestation are similar to the pattern observed with cigarette smoking where a higher risk of LBW is observed in women who continue to smoke and/or do not reduce the number of cigarettes smoked during pregnancy.[64] Currently, there is no evidence of a safe frequency, amount, and timing of cannabis use during pregnancy.

Evidence of an interaction between cannabis and smoking is still inconclusive. The prevalence of tobacco use is much higher in women that use cannabis during pregnancy[3] and both cannabis and tobacco use have independent effects on gestational age and birth weight. Therefore, the concomitant use of both drugs can result in cumulative effects on these negative neonatal outcomes and efforts should be made to reduce the exposure to both substances and to other drugs during pregnancy, even if a clear additive interaction effect is not demonstrated.

Limitations

This review has some limitations. Although we did not apply language restrictions during the search, only studies published in Portuguese, English, Spanish, or French were included in the review. However, we only excluded one study due to language constraints (one paper in Iranian). We were not able to extract data from one study,[65] due to missing data for extraction and inclusion in the meta-analysis. This was a cross-sectional study which evaluated the use of cannabis during pregnancy based on women's self-report 2 to 9 months after delivery and we do not expect this could affect the main results of this meta-analysis. To assess the quality of studies, we used the same criteria adopted in a previous review,[16] which may not have been sufficient to classify the studies as high or low quality, one of the planned subgroup analyses. The quality assessment mainly differentiated studies that used objective measures to assess exposure to cannabis and the risk of selection bias. It is not clear whether another assessment criterion would allow a better assessment of the heterogeneity of the studies. Our control group for comparison excluded women who used other illicit drug during pregnancy, but we were not able to address prescribed drugs, and there is a possibility of residual confounding. Finally, we excluded studies of populations that were nonrepresentative of the general population of pregnant women (e.g., substance use disorders and medical comorbidities), which limited the scope and the external validity of the review.

Conclusion

Cannabis is the most frequently used drug during pregnancy, and its use is independently associated with PTB, LBW, and SGA. Future studies should focus on current knowledge gaps and explore the type of use, exposure time during pregnancy, mode of use, and dosage. Services should develop targeted approaches to counseling and to provide treatment options for women with a cannabis-related diagnosis during antenatal care. Health education messages about the risks of cannabis use should be promoted, especially for women with less prenatal care, who are often the most socially vulnerable. Public policies regarding surveillance, cannabis' regulation, and how it influences its consumption should also be discussed.

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Conflict of Interest
None declared.

References

1 Observatório Europeu da Droga e da Toxicodependência. Relatório Europeu sobre Drogas 2021: Tendências e Evoluções. Luxemburgo; 2021
2 Metz TD, Borgelt LM. Marijuana use in pregnancy and while breastfeeding. Obstet Gynecol 2018;132(05):1198–1210

3 Singh S, Filion KB, Abenhaim HA, Eisenberg MJ. Prevalence and outcomes of prenatal recreational cannabis use in high-income countries: a scoping review. BJOG 2020;127(01):8–16
4 Badowski S, Smith G. Cannabis use during pregnancy and postpartum. Can Fam Physician 2020;66(02):98–103
5 Forray A. Substance use during pregnancy. F1000 Res 2016;5 (887):F1000 Faculty Rev-887
6 Thompson R, DeJong K, Lo J. Marijuana use in pregnancy: a review. Obstet Gynecol Surv 2019;74(07):415–428
7 Wilkinson ST, Yarnell S, Radhakrishnan R, Ball SA, D'Souza DC. Marijuana legalization: impact on physicians and public health. Annu Rev Med 2016;67:453–466
8 Coleman-Cowger VH, Oga EA, Peters EN, Mark K. Prevalence and associated birth outcomes of co-use of cannabis and tobacco cigarettes during pregnancy. Neurotoxicol Teratol 2018;68:84–90
9 Varner MW, Silver RM, Rowland Hogue CJ, et al; Eunice Kennedy Shriver National Institute of Child Health and Human Development Stillbirth Collaborative Research Network. Association between stillbirth and illicit drug use and smoking during pregnancy. Obstet Gynecol 2014;123(01):113–125
10 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(04):e009986-e
11 Janisse JJ, Bailey BA, Ager J, Sokol RJ. Alcohol, tobacco, cocaine, and marijuana use: relative contributions to preterm delivery and fetal growth restriction. Subst Abus 2014;35(01):60–67
12 Gray TR, Eiden RD, Leonard KE, Connors GJ, Shisler S, Huestis MA. Identifying prenatal cannabis exposure and effects of concurrent tobacco exposure on neonatal growth. Clin Chem 2010;56(09): 1442–1450
13 Schempf AH, Strobino DM. Illicit drug use and adverse birth outcomes: is it drugs or context? J Urban Health 2008;85(06):858–873
14 van Gelder MMHJ, Donders ART, Devine O, Roeleveld N, Reefhuis JNational Birth Defects Prevention Study. Using Bayesian models to assess the effects of under-reporting of cannabis use on the association with birth defects, national birth defects prevention study, 1997-2005. Paediatr Perinat Epidemiol 2014;28(05):424–433
15 Warshak CR, Regan J, Moore B, Magner K, Kritzer S, Van Hook J. Association between marijuana use and adverse obstetrical and neonatal outcomes. J Perinatol 2015;35(12):991–995
16 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(04): 713–723
17 Blencowe H, Cousens S, Chou D, et al. Born too soon: the global epidemiology of 15 million preterm births. Reprod Health 2013; 10(suppl 1):S2
18 Moher D, Liberati A, Tetzlaff J, Altman DGPRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med 2009;6(07):e1000097
19 World Health Organization. ICD-10: International Statistical Classification of Diseases and Related Health Problems: Tenth Revision. 2nd ed. Geneva: World Health Organization; 2004
20 Howson CP, Kinney MV, Born Too Soon JL. The Global Action Report on Preterm Birth. Geneva, Switzerland: WHO; 2012
21 de Onis M, Habicht JP. Anthropometric reference data for international use: recommendations from a World Health Organization Expert Committee. Am J Clin Nutr 1996;64(04):650–658
22 Martínez-Peña AA, Perono GA, Gritis SA, et al. The impact of early life exposure to cannabis: the role of the endocannabinoid system. Int J Mol Sci 2021;22(16):8576
23 El Marroun H, Brown QL, Lund IO, et al. An epidemiological, developmental and clinical overview of cannabis use during pregnancy. Prev Med 2018;116:1–5
24 Michalski CA, Hung RJ, Seeto RA, et al. Association between maternal cannabis use and birth outcomes: an observational study. BMC Pregnancy Childbirth 2020;20(01):771
25 Guyatt G, Oxman AD, Akl EA, et al. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. J Clin Epidemiol 2011;64(04):383–394
26 Mravčík V, Nechanská B, Gabrhelík R, Handal M, Mahic M, Skurtveit S. Socioeconomic characteristics of women with substance use disorder during pregnancy and neonatal outcomes in their newborns: a national registry study from the Czech Republic. Drug Alcohol Depend 2020;209:107933
27 Saurel-Cubizolles MJ, Prunet C, Blondel B. Cannabis use during pregnancy in France in 2010. BJOG 2014;121(08):971–977
28 Leemaqz SY, Dekker GA, McCowan LM, et al; SCOPE Consortium. Maternal marijuana use has independent effects on risk for spontaneous preterm birth but not other common late pregnancy complications. Reprod Toxicol 2016;62:77–86
29 Straub HL, Mou J, Drennan KJ, Pflugeisen BM. Maternal marijuana exposure and birth weight: an observational study surrounding recreational marijuana legalization. Am J Perinatol 2021;38(01): 065–75
30 Sasso EB, Bolshakova M, Bogumil D, et al. Marijuana use and perinatal outcomes in obstetric patients at a safety net hospital. Eur J Obstet Gynecol Reprod Biol 2021;266:36–41
31 Alhusen JL, Lucea MB, Bullock L, Sharps P. Intimate partner violence, substance use, and adverse neonatal outcomes among urban women. J Pediatr 2013;163(02):471–476
32 Corsi DJ, Walsh L, Weiss D, et al. Association between self-reported prenatal cannabis use and maternal, perinatal, and neonatal outcomes. JAMA 2019;322(02):145–152
33 Hayatbakhsh MR, Flenady VJ, Gibbons KS, et al. Birth outcomes associated with cannabis use before and during pregnancy. Pediatr Res 2012;71(02):215–219
34 Klebanoff MA, Wilkins DG, Keim SA. Marijuana use during pregnancy and preterm birth: a prospective cohort study. Am J Perinatol 2021;38(S 01):e146–e54
35 Luke S, Hutcheon J, Kendall T. Cannabis use in pregnancy in British Columbia and selected birth outcomes. J Obstet Gynaecol Can 2019;41(09):1311–1317
36 Mark K, Desai A, Terplan M. Marijuana use and pregnancy: prevalence, associated characteristics, and birth outcomes. Arch Women Ment Health 2016;19(01):105–111
37 Washio Y, Goldstein ND, Butler R, et al. Self-report measure as a useful tool to identify prenatal substance use and predict adverse birth outcomes. Clin Ethics 2018;13(03):137–142
38 Bada HS, Das A, Bauer CR, et al. Low birth weight and preterm births: etiologic fraction attributable to prenatal drug exposure. J Perinatol 2005;25(10):631–637
39 Chabarria KC, Racusin DA, Antony KM, et al. Marijuana use and its effects in pregnancy. Am J Obstet Gynecol 2016;215(04):506. e1–506.e7
40 Nawa N, Garrison-Desany HM, Kim Y, et al. Maternal persistent marijuana use and cigarette smoking are independently associated with shorter gestational age. Paediatr Perinat Epidemiol 2020; 34(06):696–705
41 Crume TL, Juhl AL, Brooks-Russell A, Hall KE, Wymore E, Borgelt LM. Cannabis use during the perinatal period in a state with legalized recreational and medical marijuana: the association between maternal characteristics, breastfeeding patterns, and neonatal outcomes. J Pediatr 2018;197:90–96
42 Haight SC, King BA, Bombard JM, et al. Frequency of cannabis use during pregnancy and adverse infant outcomes, by cigarette smoking status—8 PRAMS states, 2017. Drug Alcohol Depend 2021;220:108507
43 Nguyen VH, Harley KG. Prenatal cannabis use and infant birth outcomes in the pregnancy risk assessment monitoring system. J Pediatr 2022;240:87–93
44 Kharbanda EO, Vazquez-Benitez G, Kunin-Batson A, Nordin JD, Olsen A, Romitti PA. Birth and early developmental screening

outcomes associated with cannabis exposure during pregnancy. J Perinatol 2020;40(03):473–480
45 Bailey BA, Wood DL, Shah D. Impact of pregnancy marijuana use on birth outcomes: results from two matched population-based cohorts. J Perinatol 2020;40(10):1477–1482
46 Bandoli G, Jelliffe-Pawlowski L, Schumacher B, et al. Cannabis-related diagnosis in pregnancy and adverse maternal and infant outcomes. Drug Alcohol Depend 2021;225:108757
47 Burns L, Mattick RP, Cooke M. The use of record linkage to examine illicit drug use in pregnancy. Addiction 2006;101(06):873–882
48 Oni HT, Buultjens M, Mohamed AL, Islam MM. Neonatal outcomes of infants born to pregnant women with substance use disorders: a multilevel analysis of linked data. Subst Use Misuse 2022;57 (01):1–10
49 Petrangelo A, Czuzoj-Shulman N, Balayla J, Abenhaim HA. Cannabis abuse or dependence during pregnancy: a population-based cohort study on 12 million births. J Obstet Gynaecol Can 2019;41 (05):623–630
50 Shi Y, Zhu B, Liang D. The associations between prenatal cannabis use disorder and neonatal outcomes. Addiction 2021;116(11): 3069–3079
51 Bonello MR, Xu F, Li Z, Burns L, Austin MP, Sullivan EA. Mental and behavioral disorders due to substance abuse and perinatal outcomes: a study based on linked population data in New South Wales, Australia. Int J Environ Res Public Health 2014;11(05): 4991–5005
52 Almada M, Alves P, Fonseca BM, et al. Synthetic cannabinoids JWH-018, JWH-122, UR-144 and the phytocannabinoid THC activate apoptosis in placental cells. Toxicol Lett 2020; 319:129–137
53 Maia J, Almada M, Midão L, et al. The cannabinoid delta-9-tetrahydrocannabinol (THC) disrupts estrogen signaling in human placenta. Toxicol Sci 2020;177(02):420–430
54 Maia J, Fonseca BM, Cunha SC, et al. Impact of tetrahydrocannabinol on the endocannabinoid 2-arachidonoylglycerol metabolism: ABHD6 and ABHD12 as novel players in human placenta. Biochim Biophys Acta Mol Cell Biol Lipids 2020;1865(12):158807
55 Yao JL, He QZ, Liu M, et al. Effects of Δ(9)-tetrahydrocannabinol (THC) on human amniotic epithelial cell proliferation and migration. Toxicology 2018;394:19–26
56 Brown SJ, Mensah FK, Ah Kit J, et al. Use of cannabis during pregnancy and birth outcomes in an Aboriginal birth cohort: a cross-sectional, population-based study. BMJ Open 2016;6(02): e010286
57 El Marroun H, Tiemeier H, Steegers EA, et al. Intrauterine cannabis exposure affects fetal growth trajectories: the Generation R Study. J Am Acad Child Adolesc Psychiatry 2009;48(12):1173–1181
58 Fergusson DM, Horwood LJ, Northstone KALSPAC Study Team. Avon Longitudinal Study of Pregnancy and Childhood. Maternal use of cannabis and pregnancy outcome. BJOG 2002;109(01): 21–27
59 Fried PA, Watkinson B, Willan A. Marijuana use during pregnancy and decreased length of gestation. Am J Obstet Gynecol 1984;150 (01):23–27
60 Gabrhelík R, Mahic M, Lund IO, et al. Cannabis use during pregnancy and risk of adverse birth outcomes: a longitudinal cohort study. Eur Addict Res 2021;27(02):131–141
61 Howard DS, Dhanraj DN, Devaiah CG, Lambers DS. Cannabis use based on urine drug screens in pregnancy and its association with infant birth weight. J Addict Med 2019;13(06):436–441
62 Leal MD, Esteves-Pereira AP, Nakamura-Pereira M, et al. Prevalence and risk factors related to preterm birth in Brazil. Reprod Health 2016;13(suppl 3):127
63 Dean SV, Mason E, Howson CP, Lassi ZS, Imam AM, Bhutta ZA. Born too soon: care before and between pregnancy to prevent preterm births: from evidence to action. Reprod Health 2013;10(suppl 1):S3
64 Flower A, Shawe J, Stephenson J, Doyle P. Pregnancy planning, smoking behaviour during pregnancy, and neonatal outcome: UK Millennium Cohort Study. BMC Pregnancy Childbirth 2013; 13:238
65 Ko JY, Tong VT, Bombard JM, Hayes DK, Davy J, Perham-Hester KA. Marijuana use during and after pregnancy and association of prenatal use on birth outcomes: a population-based study. Drug Alcohol Depend 2018;187:72–78