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Prenatal cannabis exposure and adverse neonatal outcomes: a systematic review and meta-analysis with meta-regression on tobacco co-use

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ABSTRACT

Background Prenatal cannabis use has risen; tobacco co-use clouds its contribution to neonatal outcomes.

Objective To quantify these associations and how far between-arm tobacco imbalance explains them.

Methods Observational studies, eight databases to 20 September 2026. Random-effects models pooled tobacco-unadjusted risk ratios (RRs) and mean differences. Meta-regression used the between-arm tobacco difference, with and without study size; tobacco-balanced studies pooled separately; within-study adjusted/unadjusted pairs compared.

Results 79 studies covered about 18.2 million pregnancies. Exposure was associated with small for gestational age (SGA; RR 1.90, 1.66 to 2.17), low birth weight (LBW; 1.72, 1.47 to 2.03), perinatal mortality (1.76, 1.34 to 2.30), preterm birth (1.41, 1.25 to 1.60) and neonatal intensive care unit (NICU) admission (1.41, 1.18 to 1.67), and 166 g lower birth weight (122 to 211). Trim-and-fill raised preterm, NICU and mortality to 1.52, 1.50, 1.85; none for LBW or SGA. Associations rose with the between-arm tobacco difference for SGA, LBW, preterm and NICU ($p \leq 0.001$), independently of size. Where tobacco was balanced, they were smaller (SGA 1.35, LBW 1.38), imprecise for preterm and NICU. Multivariable adjustment including tobacco gave a within-study ratio of risk ratios of 0.78 (median 55% log-scale reduction, 31 pairs). With biologically verified exposure, LBW (1.66, 1.41 to 1.95) and SGA (1.79, 1.54 to 2.07) persisted.

Conclusions Across more studies than any previous review, cannabis exposure was associated with small for gestational age, low birth weight, preterm birth, NICU admission and perinatal mortality. When controlling for tobacco smoking, preterm birth and NICU admission were no longer significantly increased; small for gestational age and low birth weight remained raised. Perinatal mortality showed no tobacco gradient, so is not attributable to tobacco, though balanced studies were too few. Counselling should address both substances. Evidence is observational and source-study adjustment erratic; certainty is very low and further evidence is needed.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Systematic reviews have reported associations between prenatal cannabis exposure and low birth weight, small for gestational age birth, preterm delivery and neonatal intensive care unit (NICU) admission, and the most recent raised its certainty rating to moderate because those associations survived adjustment for tobacco, which the source studies almost always record as an ever-versus-never binary.

WHAT THIS STUDY ADDS

⇒ Across 79 studies, more than any previous review, the associations were largest where the cannabis and comparison arms differed most in tobacco use, a difference that accounted for a third to three fifths of the between-study variance for low birth weight, small for gestational age, preterm birth and NICU admission, while perinatal mortality showed no such gradient. Where the arms were balanced for tobacco, preterm birth and NICU admission were no longer significantly increased, whereas small for gestational age and low birth weight remained raised.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Counselling for cannabis abstinence should address tobacco at the same time and is best grounded in the effect on fetal growth. For meta-analyses of this literature, estimates already adjusted for the confounder under examination cannot contribute to a test of confounding by it, and where tobacco is reported by arm, it is the difference between the arms that carries the information.

INTRODUCTION

Cannabis is the most widely used federally controlled substance in pregnancy in North America, and self-reported prevalence has risen roughly threefold in two decades, from about 3% in 2002 to 7% to 20% in some jurisdictions by 2024.[1–3] Delta-9-tetrahydrocannabinol (THC) crosses the placenta and binds fetal cannabinoid receptors that regulate placental vascular development and

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neurodevelopment.[4 5] Given that biological plausibility, and the rising potency of available products, the American College of Obstetricians and Gynecologists (ACOG) and the Society for Maternal-Fetal Medicine (SMFM) both advise complete abstinence during pregnancy and lactation.[6]

Several systematic reviews have reported associations between prenatal cannabis exposure and low birth weight (LBW), small-for-gestational-age (SGA) birth, preterm delivery and neonatal intensive care unit (NICU) admission.[7–12] Interpreting them is difficult because tobacco is co-used by between half and nine-tenths of pregnant people who use cannabis, and maternal smoking is itself among the strongest modifiable causes of fetal growth restriction and perinatal death.[13 14] The two exposures are highly correlated, and cannabis has no established effect that tobacco does not also produce.

Existing primary studies handle this unevenly. Most adjust for tobacco only as an ever-versus-never binary recorded at a single antenatal visit, without dose, timing or biochemical confirmation, and a substantial minority do not adjust for it at all. Binary adjustment of a mismeasured confounder may leave residual confounding biased towards the exposure of interest, so previous reviews are expected to overstate the contribution of cannabis by an unknown amount. Examining that, rather than assuming it away, is the problem this review addresses.

We therefore had two aims. First, to estimate the association between prenatal cannabis exposure and neonatal outcomes in the largest available body of observational evidence. Second, to examine how far it varies with tobacco co-use, by testing whether effect sizes track the difference in tobacco prevalence between the cannabis-exposed and comparison arms,[15] and by comparing studies that balance tobacco between their arms against those that do not.

METHODS

This review was pre-registered on PROSPERO (CRD420251065325) and amended on 21 and 30 September 2026 to record the expanded search, the full re-extraction and the analyses specified after it began, identified as post-hoc below. Reporting follows Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020[16] and the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) guideline for observational studies.[17]

Search strategy and selection criteria

We searched Ovid MEDLINE(R) ALL, Ovid Embase, Cochrane CENTRAL, CINAHL Plus with Full Text, APA PsycINFO, Web of Science Core Collection, Scopus and LILACS from database inception to 20 September 2026, without language restriction, combining controlled vocabulary (MeSH and Emtree) with free-text terms for pregnancy AND cannabis AND neonatal outcomes. Grey literature was searched through the first 200 relevance-ranked records in Google Scholar, ClinicalTrials.gov, the WHO ICTRP and OpenAlex dissertations. The full strategy, with the result count of every line, is in online supplemental file 2.

Titles, abstracts and full texts were each screened independently by two reviewers, with a third (GJM) resolving disagreements. We included primary observational studies (cohort, case-control, cross-sectional) comparing neonatal outcomes in pregnancies with any prenatal cannabis exposure against no exposure, requiring an unexposed comparison group and at least one prespecified outcome. Randomised trials were excluded on ethical grounds. Reference lists of included studies and prior reviews were hand-searched.

Data extraction and quality assessment

Two reviewers independently extracted data using a piloted form, blind to one another and to the working dataset, collecting study characteristics, participant demographics, the method of exposure ascertainment (self-report, a biological assay or a diagnostic code in administrative data), tobacco co-use prevalence in each arm, and outcome data with adjusted and unadjusted estimates where available. The same two reviewers scored study quality and rated certainty independently; they agreed on every figure in 62 of the 116 outcome cells they shared, and Newcastle-Ottawa totals fell within one point for all 38 studies both scored. A third reviewer (GJM) adjudicated each against the source table (online supplemental table S2).

Because the central analysis relates each study's estimate to the difference in tobacco use between its arms, the contributed estimate could not itself have had tobacco removed by adjustment. We took the unadjusted estimate where one was reported, and otherwise an estimate adjusted only for covariates excluding tobacco. Of the 162 binary contributions, 135 from 54 studies come from printed cell counts and are therefore crude; the other 27, from 11 studies, were entered through counts reconstructed from a reported ratio, which the counts-only analysis in online supplemental table S7 removes. Estimates from models containing a tobacco term were not pooled; where a study reported both, the pair entered the within-study analysis below. Studies that removed tobacco by design or balanced it by matching or weighting were pooled, their between-arm difference recorded after that step. Where two reports drew on the same source population over overlapping periods, the one with the larger non-overlapping contribution was kept.

Risk of bias was assessed with the Newcastle-Ottawa Scale (NOS) for cohort and case-control studies,[18] scoring 8 or 9 as good, 7 as fair and 6 or below as poor. 38 of the 79 contributing studies were scored independently by two reviewers for this revision; the provenance of every other assessment, including

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those carried forward from the original review, is stated in online supplemental table S3.

Statistical analysis

Analyses used a purpose-written Python implementation of the standard random-effects methods (NumPy and SciPy),[19] reproduced independently in R with metafor,[20] all 81 quantities agreeing; both are in the replication package. Random-effects models fitted by restricted maximum likelihood with the Hartung-Knapp-Sidik-Jonkman variance adjustment pooled risk ratios (RRs) for dichotomous and mean differences (MDs) for continuous outcomes with 95% CIs; the same estimator and adjustment were used for every meta-regression. A continuity correction of 0.5 was added only to studies with a zero cell, metafor's default. Ratios reported without counts were entered through reconstructed cell counts reproducing them exactly, never added to participant totals. ORs were entered as approximations to risk ratios, and one study's events per person-week as a crude incidence-rate ratio. Standard errors came from an exact p value or a whole-sample SD where no other measure of spread was given.[21] Heterogeneity was quantified by tau-squared and I-squared. Certainty was assessed with GRADE (Grading of Recommendations, Assessment, Development, and Evaluation)[22] by two independent reviewers (SM and DGH).

The pre-specified outcomes were low birth weight (<2500 g), small for gestational age (SGA, typically <10th centile), preterm birth (<37 weeks), NICU admission, perinatal mortality (stillbirth plus neonatal death), birth weight (g), gestational age at delivery (weeks), birth length (cm) and head circumference (cm). Univariable meta-regression explored four study-level moderators: tobacco prevalence in the cannabis-exposed arm, the difference in that prevalence between the arms, mean maternal age and the percentage reporting alcohol use. The between-arm difference, specified post-hoc, is the covariate of primary interest: it measures how far apart the arms are on tobacco rather than how much either smokes, which is how residual confounding by tobacco would act. Significant coefficients were refitted with the base-ten logarithm of total participants as a second covariate. Outcomes were pooled only where the source definition matched ours; near misses such as special care nursery admission, intrauterine growth restriction and SGA below the fifth centile were not substituted, though stillbirth or fetal death counted as perinatal mortality.

Sensitivity analyses repeated every pooled estimate and meta-regression by exposure ascertainment (biologically verified, self-reported and excluding diagnostic codes), by publication period (from 2000 onward, and before 2025), with leave-one-out ranges and, for Nguyen 2022,[13] the any-cannabis contrast. Two further restrictions, also post-hoc, test where the pooled evidence is least independent of itself: one removes the two contributions whose populations nest inside others, a national inpatient sample for 1999 to 2013 and a Californian health-plan cohort for 2011 to 2019; the other removes every study entered through cell counts reconstructed from a reported ratio, which is the set holding every OR and the single incidence-rate ratio (online supplemental table S7). The diagnostic-code restriction was post-hoc because such studies sample the severe end of exposure and the high end of the tobacco differential. Studies balancing tobacco to within 10 percentage points were pooled separately and compared with the rest. Conference abstracts were eligible but not pooled. Small-study effects were assessed for outcomes with 10 or more studies by funnel plots, Egger's test and trim-and-fill.

As a secondary analysis addressing the same question from within studies, we identified every included study reporting both a tobacco-adjusted and a tobacco-unadjusted estimate for the same outcome and population, and pooled the ratio of the two on the log scale. That quantity is a ratio of risk ratios: it says how far adjustment moves the risk ratio, not what share of the association it removes, because the null of a risk ratio is one and not zero. It also measures whatever separates the two models, which is the tobacco term alone in only five pairs and a whole covariate set in the rest. The share removed was computed per pair as the proportional reduction in the excess risk and in the log risk ratio, and reported descriptively, since both divide by a quantity that vanishes near the null. The variance of a paired log ratio is $sa^2 + su^2 - 2\rho sa{\cdot}su$, and ρ is not recoverable from a published report, so the pooled ratio was refitted across ρ from 0 to 0.9; because the pairs cluster in 15 studies the interval is cluster-robust on study, and the pooled ratio was also repeated with one pair per study and leaving out each study in turn (online supplemental table S6).

RESULTS

Study selection, characteristics and risk of bias

The searches identified 9410 records from the eight databases and 532 through other methods. After removing 5689 duplicates and 131 registry records with no posted results, 4122 were screened at title and abstract, 202 reports were sought and 183 assessed in full text (figure 1).

103 reports met the inclusion criteria.[13 14 23–130] Their general characteristics, with the 79 contributing studies identified, are given in online supplemental table S1. A further seven were sought but could not be obtained and are named there and in the note to online supplemental table S2. 79 studies, drawn from 75 source populations, contribute data to at least one pooled outcome, four populations through two reports each. They were published between 1982 and 2026 and encompass about 18.2 million pregnancies, about 180 000 of them cannabis-exposed. Of them, 39 verified exposure biologically, 35 relied on self-report and five on a diagnostic code, and 61 reported

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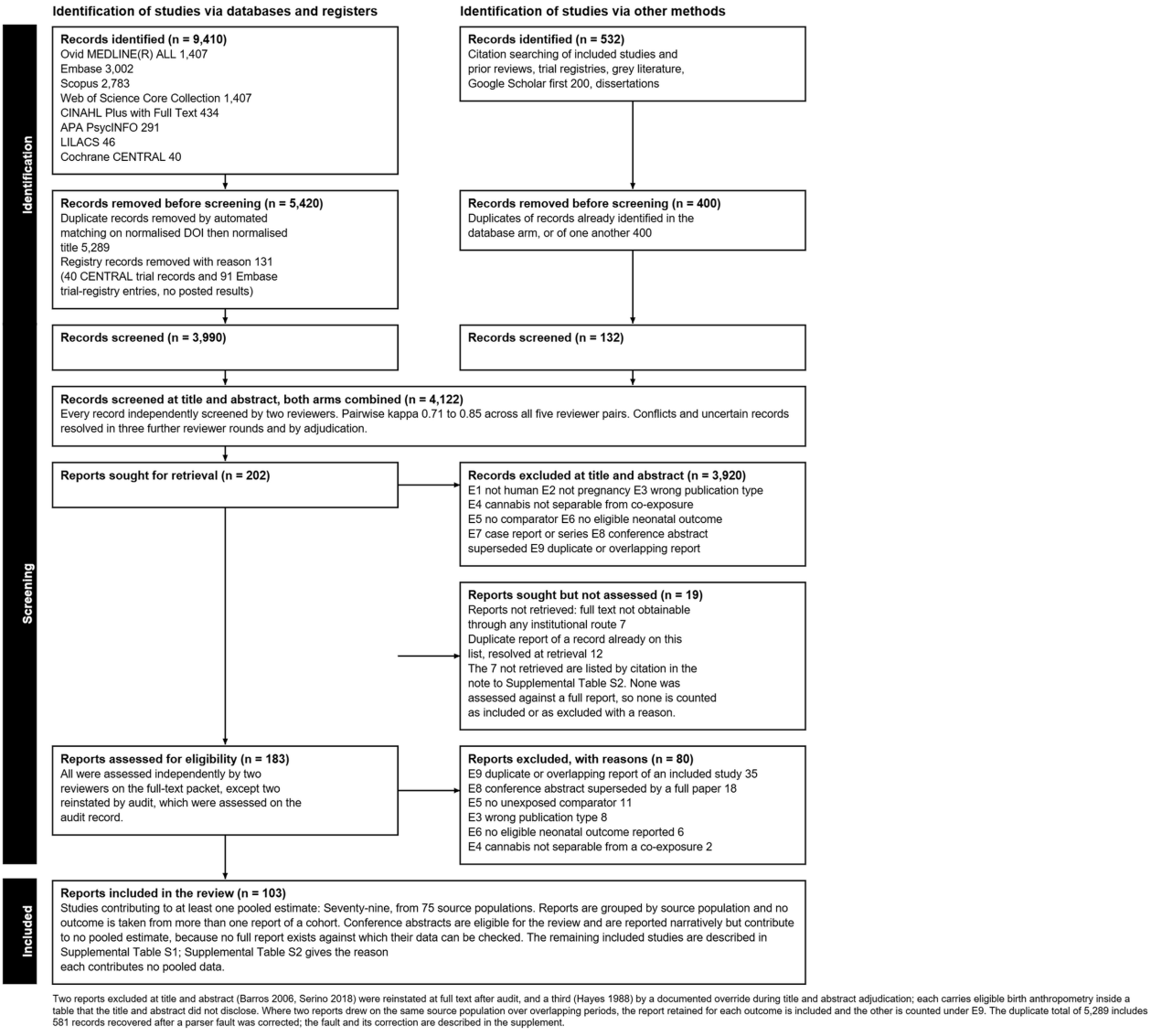

Figure 1 PRISMA 2020 flow diagram. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

tobacco use in both arms. The 24 included reports contributing no pooled data are listed with reasons in online supplemental table S2.

The 79 contributing studies had a mean NOS score of 7.3 (median 7, range 5 to 9): 34 good, 32 fair and 13 poor (online supplemental table S3).

Pooled associations

Prenatal cannabis exposure was associated with every outcome examined. Risks were raised for low birth weight (RR 1.72, 1.47 to 2.03, 35 studies) and small for gestational age (1.90, 1.66 to 2.17, 33 studies), the largest categorical effect (figure 2), and for preterm birth (1.41, 1.25 to 1.60, 48 studies), NICU admission (1.41, 1.18 to 1.67, 28 studies) and perinatal mortality (1.76, 1.34 to 2.30, 18 studies), which had the least heterogeneity (figure 3). Heterogeneity was high throughout (I^2 74% to 98%; table 1).

The continuous measures moved the same way (figure 4). Mean birth weight was 166 g lower in the exposed group (95% CI −211 to −122, 39 studies), gestational age 0.18 weeks shorter (0.05 to 0.30, 35 studies), birth length 0.90 cm shorter (0.54 to 1.26, 16 studies) and head circumference 0.34 cm smaller (0.06 to 0.61, 16 studies).

Trim-and-fill imputed studies for four outcomes, on the side of larger effects for three: seven for preterm birth, three for perinatal mortality and three for NICU admission, taking those to 1.52, 1.85 and 1.50. For head circumference, it imputed three on the side of smaller, taking −0.34 cm to −0.20 cm. It imputed none for the other five outcomes (online supplemental figure S1, online supplemental table S5).

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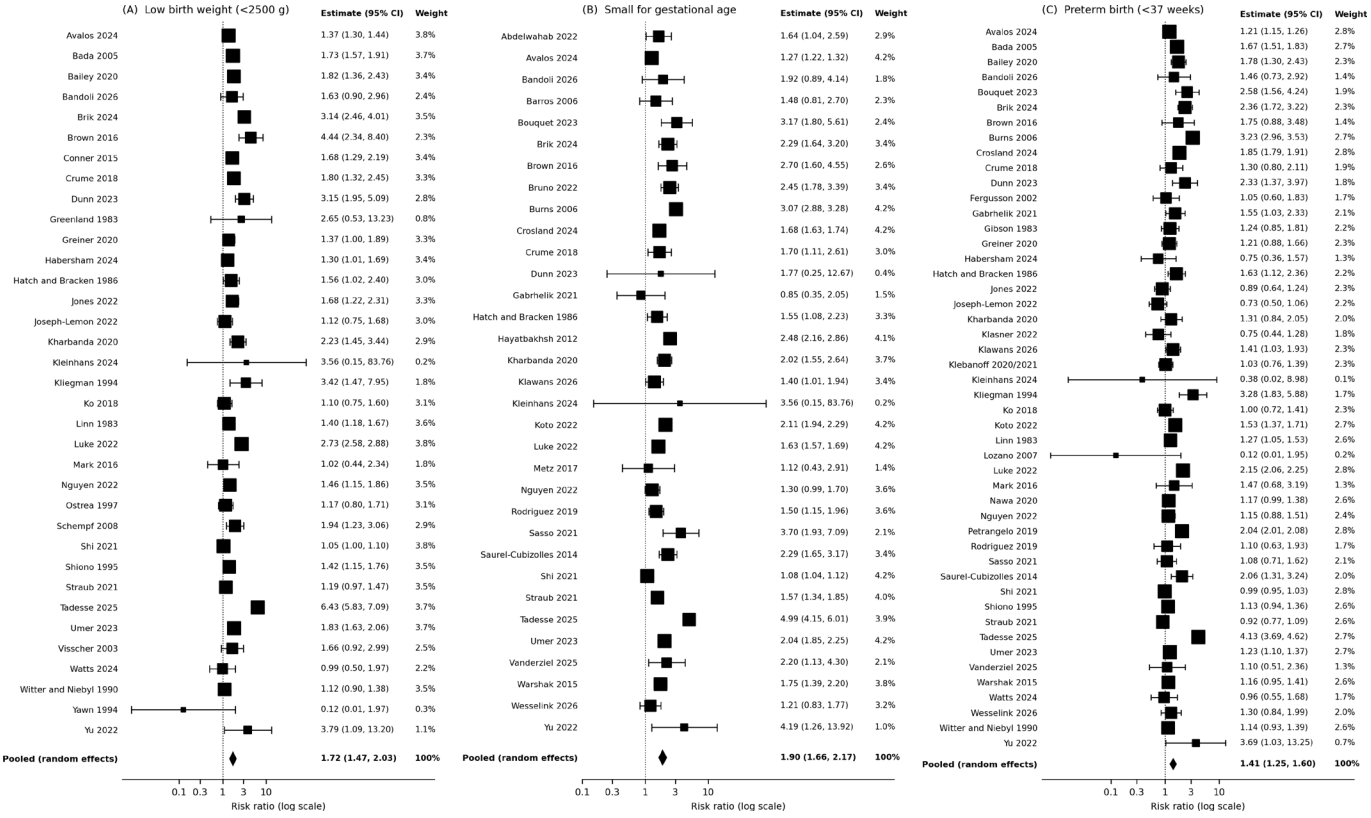

Figure 2 Forest plots of low birth weight (A), small for gestational age (B) and preterm birth (C).

Tobacco co-use

Tobacco prevalence in the cannabis-exposed arm, the covariate previous reviews have used, explained part of the between-study variance for small for gestational age (p=0.002, 38%), NICU admission (p=0.004, 35%) and preterm birth (p=0.01, 9%), and was not significant for low birth weight (p=0.06) or birth weight (p=0.03) (online supplemental table S4).

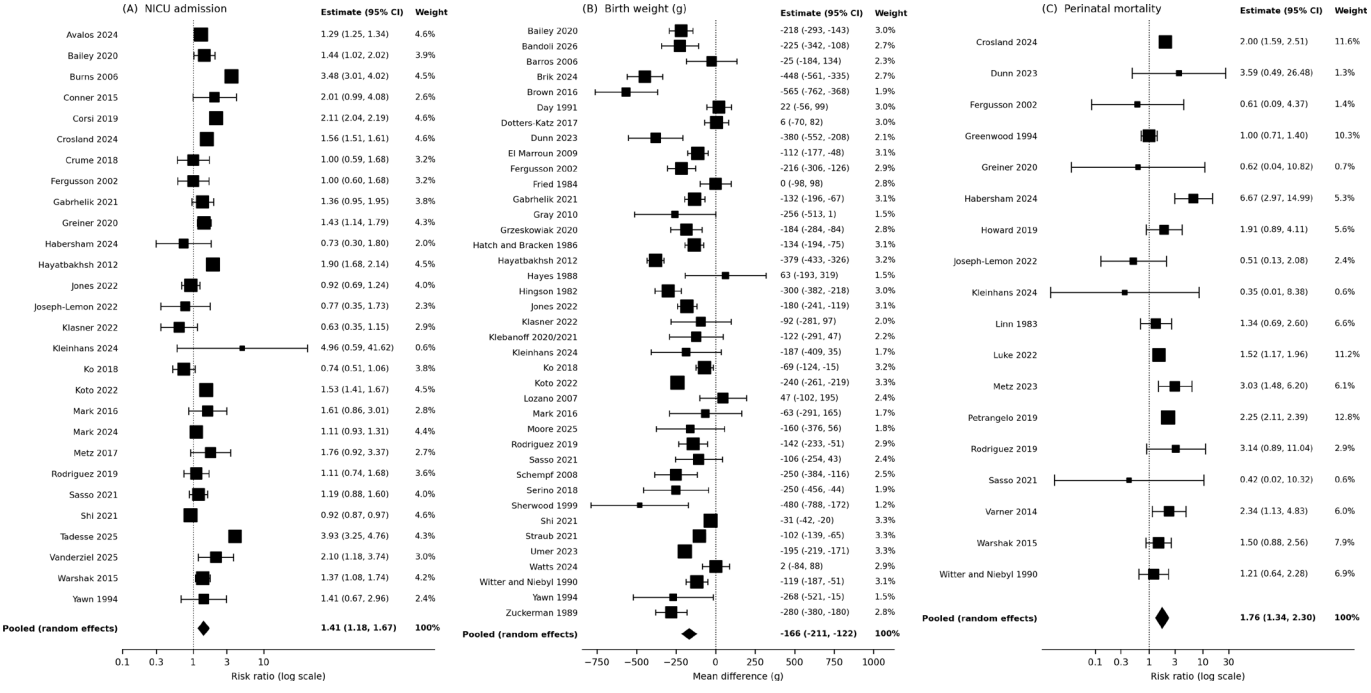

Figure 3 Forest plots of NICU admission (A), birth weight (B) and perinatal mortality (C). NICU, neonatal intensive care unit.

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Table 1 GRADE summary of findings: prenatal cannabis exposure compared with no exposure for neonatal outcomes

Outcome	Participants (studies)	Relative effect (95% CI)	Anticipated absolute effect	Certainty
Small for gestational age (<10th centile)	5 443 200 (33)	RR 1.90 (1.66 to 2.17)	72.7 more per 1000 (53.4 to 94.9 more) with a comparator risk of 81.2 per 1000	Very low
Low birth weight (<2500 g)	1 879 314 (35)	RR 1.72 (1.47 to 2.03)	26.5 more per 1000 (17.0 to 37.6 more) with a comparator risk of 36.6 per 1000	Very low
Preterm birth (<37 weeks)	18 098 411 (48)	RR 1.41 (1.25 to 1.60)	28.3 more per 1000 (17.3 to 40.7 more) with a comparator risk of 68.1 per 1000	Very low
NICU admission	4 988 642 (28)	RR 1.41 (1.18 to 1.67)	37.5 more per 1000 (16.8 to 62.1 more) with a comparator risk of 92.0 per 1000	Very low
Perinatal mortality	16 852 875 (18)	RR 1.76 (1.34 to 2.30)	3.9 more per 1000 (1.8 to 6.8 more) with a comparator risk of 5.2 per 1000	Very low
Birth weight (g)	301 198 (39)	Not applicable	Mean difference −166.2 g (−210.6 to −121.7)	Very low
Gestational age at delivery (weeks)	248 826 (35)	Not applicable	Mean difference −0.178 weeks (−0.304 to −0.052)	Very low
Birth length (cm)	137 767 (16)	Not applicable	Mean difference −0.904 cm (−1.265 to −0.543)	Very low
Head circumference (cm)	138 029 (16)	Not applicable	Mean difference −0.335 cm (−0.607 to −0.064)	Very low

Pooled with random-effects models, restricted maximum likelihood and the Knapp-Hartung adjustment. Comparator risks are the pooled event rate in the unexposed arms of the contributing studies. Reasons for each rating, together with heterogeneity, small-study effects and the tobacco meta-regression result for each outcome, are given in online supplemental table S5. Preterm birth and perinatal mortality were re-rated by two reviewers on the revised data.
GRADE, Grading of Recommendations, Assessment, Development, and Evaluation; NICU, neonatal intensive care unit; RR, risk ratio.

The difference in tobacco prevalence between the arms explained more. Each 10-percentage-point widening multiplied the risk ratio by 1.15 for low birth weight (95% CI 1.07 to 1.23, p=0.0006, 43% of between-study variance), 1.12 for small for gestational age (1.07 to 1.18, p<0.0001, 59%), 1.11 for preterm birth (1.06 to 1.17, p<0.0001, 32%) and 1.16 for NICU admission (1.07 to 1.24, p=0.0004, 50%), and lowered birth weight by a further 31 g (p=0.002, 24%) (figure 5). The difference is uncorrelated with study size (r=0.13, p=0.36), every coefficient held when the logarithm of study size was added (p≤0.0007), and all five survived leave-one-out analysis (worst case p=0.024) (online supplemental table S4).

Gestational age (p=0.05), head circumference (p=0.03) and perinatal mortality (p=0.21) showed no gradient, and the coefficient for birth length (p=0.04) rests on 12 studies and did not survive adjustment for study size. The studies that balanced tobacco to within 10 points gave smaller associations: small for gestational age 1.35 (1.08 to 1.69), low birth weight 1.38 (1.12 to 1.70), preterm birth 1.18 (0.90 to 1.55) and NICU admission 1.16 (0.80 to 1.68), against 2.00, 1.79, 1.46 and 1.50 in the rest. Only the small for gestational age contrast was significant on its own (p=0.03). Birth weight was 93 g lower in the balanced studies (−209 to 24) against 154 g in the rest (p=0.26).

Restricting by how exposure was ascertained changed the gradient more than the associations (online supplemental table S7). Among the 39 studies that verified exposure biologically, the associations remained: low birth weight 1.66 (1.41 to 1.95), small for gestational age 1.79 (1.54 to 2.07), preterm birth 1.32 (1.10 to 1.59), NICU admission 1.25 (1.11 to 1.42) and birth weight

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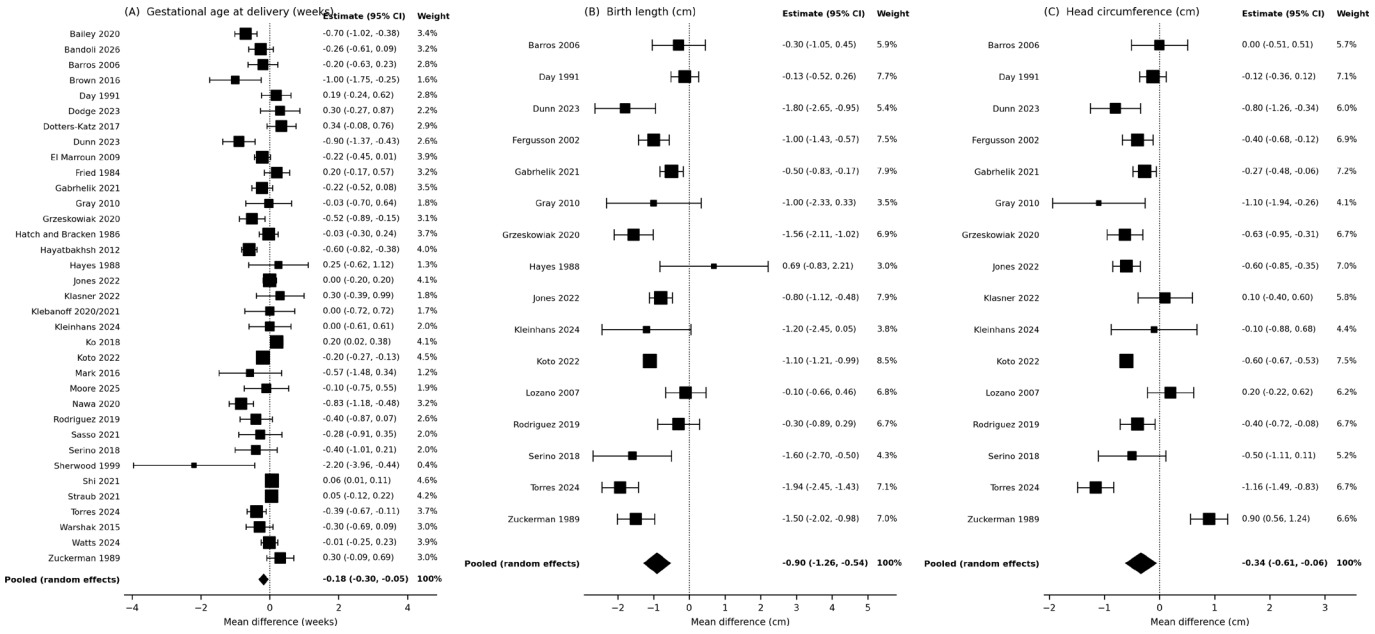

Figure 4 Forest plots of gestational age at delivery (A), birth length (B) and head circumference (C).

−176 g (−235 to −117). In these, the tobacco gradient was present only for small for gestational age, although their differentials spanned the same range, whereas in the 35 self-report studies, it was present for most outcomes. Removing the five diagnostic-code studies weakened every gradient but left all five significant and lowered the pooled estimates by 4% to 7%. Publication period, the any-cannabis contrast for Nguyen 2022 and leave-one-out analysis changed no conclusion.

Neither restriction for dependence changed the results. Removing the two contributions whose populations nest inside others left low birth weight at 1.74, small for gestational age at 1.93, preterm birth at 1.41, NICU admission at 1.41 and perinatal mortality at 1.70, with every tobacco gradient intact (p≤0.001). Removing the studies entered through a reconstructed ratio, which takes out every OR and the incidence-rate ratio and leaves 68, gave 1.74, 1.96, 1.42, 1.40 and 1.82, with the gradients stronger rather than weaker (33% to 65% of variance).

15 studies reported both a tobacco-adjusted and a tobacco-unadjusted estimate for the same outcome and population, giving 41 pairs, four not on the harmful side of the null and so not pooled (online supplemental table S6). The remaining 37 give a ratio of risk ratios of 0.782, with a cluster-robust interval on the 15 studies of 0.709 to 0.862; refitting across the whole range of within-pair correlation moves the point estimate only between 0.774 and 0.786, one pair per study gives 0.767 (0.687

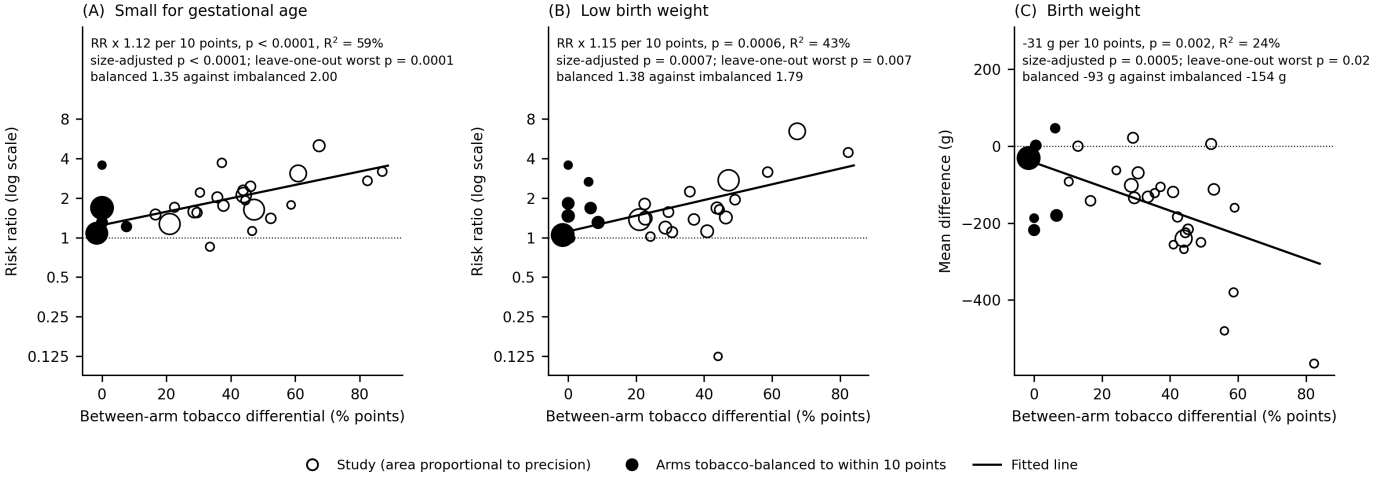

Figure 5 Meta-regression on the between-arm tobacco differential. (A) Small for gestational age. (B) Low birth weight. (C) Birth weight. Filled circles are the studies that balance tobacco between their arms to within ten percentage points. Circle area is proportional to study precision. RR, risk ratio.

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to 0.857) and leaving out each study in turn gives 0.760 to 0.826. This adjustment moves the risk ratio down by about a fifth; the share of the association it removes is larger and more variable, a median reduction of 55% in the log risk ratio (range −29% to 114%) and 64% in the excess risk across the 31 pairs where it can be computed. Only five pairs, from two studies, differ by the tobacco term alone and pool to 0.890 (0.796 to 0.996).

Certainty of evidence

Certainty is summarised in table 1, rated independently by two reviewers. All contributing studies are observational, so each started at low and fell to very low for risk of bias from residual tobacco confounding and for inconsistency. Neither reviewer applied an upgrade: the balanced and verified subgroups are supportive but establish neither that confounding would only reduce the association nor a dose-response gradient.

DISCUSSION

We set out to do two things. The first was to estimate the association in the largest body of observational evidence yet assembled, 79 studies; exposure was associated with every outcome examined, consistent with earlier reviews.[7–12] The second was to examine how far that association varies with tobacco imbalance between the arms, and it varies strongly for four of the five categorical outcomes. The method is study-level meta-regression[15]; what is new is the covariate and the eligibility rule. We regress on the difference in tobacco prevalence between the arms rather than on prevalence in the exposed arm, and no estimate that had already had tobacco removed enters any pooled result, which is what makes a gradient on that difference interpretable.

Interpretation in the context of other evidence

The central finding is that the associations are largest where the two arms differ most in tobacco use. Each 10-point widening of the tobacco gap raised the risk ratio by 11% to 16% for low birth weight, small for gestational age, preterm birth and NICU admission, and the gap explained a third to three fifths of the between-study variance, independently of study size. Previous reviews could not see this because they regressed on prevalence in the exposed arm, which cannot detect confounding: a study in which both arms smoke heavily is not confounded, whereas one in which only the cannabis arm smokes is. On that covariate, the signal is weaker and inconsistent.

The contrast with the most recent review is instructive. Lo and colleagues, updating a living review to April 2024, pooled 51 studies and more participants than we do, and reported adjusted ORs of 1.75 for low birth weight, 1.52 for preterm birth and 1.57 for small for gestational age, raising their certainty to moderate because those associations survived tobacco adjustment.[11] Our estimates are of the same order, so the disagreement is about what surviving adjustment shows. The estimates they pooled came from the source studies' own multivariable models, in which tobacco almost always enters as an ever-versus-never binary recorded once, and that is the adjustment our paired comparison measures: within studies, it removes a median of about half the association, ranging from strengthening one to removing all of it. An association still present after an adjustment that erratic is weak evidence of independence from tobacco, and the variability is itself a reason not to treat such adjusted estimates as comparable. A smaller 2025 meta-analysis found no significant association with preterm birth or NICU admission.[12]

Where tobacco was balanced, the associations were smaller, significantly so only for small for gestational age; for preterm birth and NICU admission, the balanced estimates were no longer distinguishable from the null, which is not the same as showing that little risk remains, since those subgroups hold six and 10 studies. Several balanced studies separate the exposures within one population by comparing cannabis-only users with women who used neither, and are not uniform: in Nguyen 2022, cannabis alone carried 1.30 for small for gestational age against 2.33 for cigarettes alone, and in Crosland 2024[43], 1.85 for preterm birth.

The gradient should not be over-read. Heavy-use and use-disorder populations anchor one end and studies that removed tobacco by design the other, and the covariate can stand in for anything that travels with it. More instructive is the split by exposure measurement. In the 39 studies that verified exposure biologically, the associations persisted but the tobacco gradient was present only for small for gestational age, whereas in the 35 self-report studies, it was present for most outcomes over the same tobacco range.

None of this supports a single tobacco-adjusted pooled estimate; extrapolating the fitted line to a gap of zero rests on the few studies near that point, and a study-level covariate cannot identify how much of an effect a confounder causes. Studies that verified exposure biologically are a separate matter: they show the growth association is not an artefact of self-report, and say nothing about tobacco, which is not balanced in them. Perinatal mortality showed no gradient and too few balanced studies to interpret.

Strengths and limitations

Strengths include scale, prospective PROSPERO registration, a search across eight databases without language restriction, duplicate independent screening of every record, verification of every extracted effect estimate against the source table, a rule keeping tobacco-adjusted estimates out of the pool, sensitivity analyses by exposure ascertainment, and leave-one-out analysis of every significant meta-regression coefficient.

Limitations include high heterogeneity, reliance in about half the studies on self-report, and residual confounding from socioeconomic factors, polysubstance use or care. Meta-regression is ecological and

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cannot replace individual-level adjustment, and the gradient could partly reflect other characteristics that travel with tobacco imbalance. ORs were pooled as approximations to risk ratios, which overstates the risk ratio where the outcome is common; restricting to studies that printed counts changed nothing. Contributions mix crude estimates with estimates adjusted for covariates other than tobacco, counted here for the binary outcomes but not study by study for the continuous ones, and differing covariate sets could themselves move effect sizes. The 18.2 million pregnancies sum the contributing studies' samples, each cohort counted once, and are an upper bound: duplication within the Californian birth registry was resolved by period, but a national administrative sample for 1999 to 2013 overlaps it. Few studies reported dose, timing or potency. The seven unretrieved reports are a further limitation, though the three with results in their abstracts give only smoking-adjusted estimates. Trim-and-fill suggests the missing studies report larger effects for preterm birth and perinatal mortality, though head circumference runs the other way. Most studies came from high-income North American or European settings.

Implications for practice, policy and future research

These results are consistent with the advice of ACOG and SMFM to avoid cannabis in pregnancy,[6] but move its emphasis to fetal growth, which is a firmer basis for counselling than the categorical risks usually quoted. Because the two exposures travel together, counselling that addresses cannabis without tobacco will miss much of the risk, and public health messaging should treat co-use as usual.

Priority for future research should go to individual-participant-data meta-analyses that adjust for tobacco at the individual level, to prospective cohorts with serial biological verification and characterisation of dose, timing and potency, and to mechanistic work on high-THC products. For meta-analyses of this literature, three things follow. Pooled estimates should come from models that have not already adjusted for the confounder under examination. Where tobacco is reported by arm, it is the difference between the arms that carries the information, not prevalence in the exposed arm. And studies in which the arms are balanced, or the exposures separated by design, should be pooled and reported separately.

CONCLUSION

This is the largest synthesis of this question to date by number of studies and of included reports. In it, prenatal cannabis exposure was associated with every outcome examined: small for gestational age birth, low birth weight, preterm birth, admission to neonatal intensive care and perinatal mortality, together with reductions in mean birth weight, birth length, gestational age at delivery and head circumference.

Much of that association is attributable to tobacco. The wider the difference in tobacco use between the exposed and comparison arms, the larger every one of those associations became, and that difference accounted for between a third and three fifths of the between-study variance. In the studies reporting both an unadjusted and an adjusted estimate, adjustment for a covariate set that included tobacco removed a median of about half of the association.

When tobacco smoking was controlled for, the outcomes separated. In the studies whose arms were balanced for tobacco, preterm birth and admission to neonatal intensive care were no longer significantly increased, whereas small for gestational age birth and low birth weight remained increased. Both associations persisted in the studies that ascertained exposure biologically rather than by self-report, so neither is an artefact of under-reporting. Restricted fetal growth is therefore the association that withstands tobacco control, and it does so as the proportion of infants born small rather than as the group mean: the mean birth weight difference in those studies was smaller and no longer significant.

Perinatal mortality is the exception. Alone among the outcomes, its association showed no gradient with between-arm tobacco imbalance, so tobacco does not account for it. Only three tobacco-balanced studies reported mortality and their pooled estimate is too imprecise to interpret, so the excess cannot be confirmed directly under tobacco control.

A further finding concerns the literature rather than the clinic. Tobacco adjustment in the source studies is not dependable: across the pairs available for comparison, it ranged from strengthening an association to removing it entirely. An association that persists after adjustment of that variability is weak evidence of independence from tobacco, which is why we rate the certainty of this evidence very low where the most recent review rated it moderate.

Counselling for cannabis abstinence remains appropriate, should address tobacco at the same time and is best grounded in the effect on fetal growth. Because every included study is observational, heterogeneity is high, the tobacco-balanced subgroups are small and the adjustment applied in the source studies is erratic, certainty remains very low and further evidence is needed. The proportion of the remaining association that tobacco causes cannot be determined from study-level data.

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Contributors GJM conceived the review and is the guarantor. GJM and KS designed the protocol and registered it with PROSPERO. DGH, MR, SM and BO screened titles, abstracts and full texts in duplicate; GJM adjudicated

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disagreements. DGH and SM extracted data independently and assessed risk of bias with the Newcastle-Ottawa Scale; GJM adjudicated extraction conflicts. SM and DGH independently rated certainty of evidence using GRADE. GJM performed the statistical analysis. KS provided neonatology expertise and supervised interpretation. EK, MK and FI carried out data collection and recording, contributed to the investigation and performed the initial data analysis. GJM drafted the manuscript; all authors revised it critically and approved the submitted version.

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