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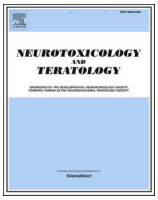

The association between prenatal cannabis use and congenital birth defects in offspring: A cumulative meta-analysis

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ABSTRACT

Objective: To examine the association between prenatal cannabis use and structural birth defects in exposed offspring.

Methods: In line with the preregistered protocol (PROSPERO: CRD42022368623), we systematically searched PubMed/Medline, CINHAL, EMBASE, Web of Science, ProQuest, Psych-Info, and Google Scholar for published articles until 25 January 2024. The methodological quality of the included studies was appraised by the Newcastle-Ottawa Quality Assessment Scale (NOS). A meta-analysis was carried out to report the pooled effect estimates from the included studies. We further performed subgroup, leave-one-out sensitivity, and meta-regression analyses, which increased the robustness of our findings.

Results: In this cumulative meta-analysis, thirty-six observational studies, consisting of 18 case-control and 18 cohort studies, with 230, 816 cases of birth defects and 18,049,013 controls (healthy babies) were included in the final analysis. We found that offspring exposed to maternal prenatal cannabis are at greater risks of a wide range of structural birth defects: cardiovascular/heart [OR = 2.35: 95 % CI 1.63 – 3.39], gastrointestinal [OR = 2.42: 95 % CI 1.61 – 3.64], central nervous system [OR = 2.87: 95 % CI 1.51 – 5.46], genitourinary [OR = 2.39: 95 % CI 1.11 – 5.17], and any (unclassified) birth defects [OR = 1.25: 95 % CI 1.12 – 1.41].

Conclusion: The findings from the current study suggest that maternal prenatal cannabis exposure is associated with a higher risk of different forms of structural birth defects in offspring. The findings underscore the significance of implementing preventive strategies, including enhanced preconception counselling, to address cannabis use during pregnancy and mitigate the risk of birth defects in offspring.

1. Introduction

Cannabis use during pregnancy has emerged as a crucial factor influencing in-utero fetal body system development (Torfs et al., 1994; van Gelder et al., 2014; Koto et al., 2022). This lifestyle choice has gained attention due to its potential impact on offspring health. According to a systematic review by Singh et al. (2020), maternal cannabis use during pregnancy has seen an increasing prevalence in recent decades, with substantial variation (min-max: 0.24-22.6%) and the highest reported use occurring in the first trimester (Singh et al., 2020). Considering this trend, it becomes imperative to assess potential harms and implement measures to mitigate these impacts on offspring who were prenatally exposed. Birth defects, structural or functional abnormalities present from birth (WHO, 2010; WHO, 2020), are a significant concern globally, with World Health Organization (WHO) estimating that approximately 240,000 newborns die annually within 28 days of birth due to congenital birth defects (WHO, 2023). These defects are often intricate and multifaceted, involving genetic, environmental, and lifestyle factors (Koto et al., 2022; WHO, 2010; WHO, 2023; WHO, CDC, 2020; Hackshaw et al., 2011). This study seeks to explore the specific association between prenatal cannabis use and congenital birth defects, addressing a critical gap in understanding the potential risks posed by this lifestyle choice during pregnancy.

While several studies have reported associations between prenatal

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cannabis use and various forms of congenital birth defects (Koto et al., 2022; Chawla, 2018; Cornelius et al., 1995; Luke et al., 2022; Siega-Riz et al., 2020), including Atrial Septal Defects (ASD) (Forrester and Merz, 2006), any congenital heart defects (CHD) (Patel and Burns, 2013), Ventricular Septal Defects (VSD) (Forrester and Merz, 2006; Williams et al., 2004), Neural Tube Defects (NTD) (van Gelder et al., 2014), Teratology of Fallot (TOF), Gastroschisis (abdominal wall defects) (van Gelder et al., 2014; David et al., 2014; Bourque et al., 2021), orofacial defects (eye, cleft lip, cleft lip + palate, and cleft palate) (van Gelder et al., 2014), and genitourinary defects (hypospadias) in exposed offspring, other studies have reported null associations (Kharbanda et al., 2020; van Gelder et al., 2009; Shaw et al., 1996; Wilson et al., 1998; Linn et al., 1983). Additionally, a meta-analysis conducted by Delker et al. reported an association between prenatal cannabis use and birth defects, with a pooled unadjusted odds ratio (OR) of 1.33 and a 95% confidence interval (CI) of 1.14–1.56 (Delker et al., 2023), based on a limited number of studies (n = 23). However, this meta-analysis did not include a significant number of epidemiological research published on the subject (Cornelius et al., 1995; Luke et al., 2022; Siega-Riz et al., 2020; Patel and Burns, 2013; David et al., 2014; Shaw et al., 1996; Wilson et al., 1998; Bandy et al., 2018; Bouquet et al., 2023; Mac Bird et al., 2009; Weinsheimer and Yanchar, 2008), which demands the application of cumulative meta-analysis (CMA) that updates the results of an existing meta-analysis to incorporate new study results (Clarke et al., 2014; Kulinskaya and Mah, 2022). CMA potentially presents time-varying evidence by systematically incorporating each study as it becomes available, offering an ongoing, real-time synthesis of emerging evidence (Braver et al., 2014; Shojania et al., 2007). Further, the study by Delker et al. did not include any grey literature, as highlighted by Conn et al. and Hopewell et al., which could reduce the risk of publication bias (Hopewell et al., 2005; Conn et al., 2003). These limitations emphasize the need for an updated study to address these gaps and provide a more comprehensive understanding of the association between prenatal cannabis use and birth defects.

Therefore, we aimed to conduct a cumulative meta-analysis, incorporating the conventional meta-analysis, to investigate the extent and adequacy of the existing literature that examined the association between prenatal cannabis use and congenital birth defects in offspring. Further this CMA enhances accuracy, reliability, and captures the evolving nature of research, examination of temporal trends, enabling understanding of variations in outcomes over time, ensuring our conclusions are current and reflect the latest developments, surpassing static analyses used in conventional systematic reviews.

2. Methods

2.1. Research design and protocol registration

The study protocol of this meta-analysis preregistered in the Prospective Register of Systematic Reviews (PROSPERO) (Registration number: CRD42022368623*)*.

We conducted this meta-analysis following the standards of the Preferred Reporting Items for Systematic Review and Meta-analyses (PRISMA-2020) (Page et al., 2021). The PRISMA-2015 statement was used to report the findings of the study (*Suppl. File 1*).

2.2. Inclusion and exclusion criteria

The inclusion criteria were developed based on the patient/population, exposure, comparison, and outcomes (PECO) format. All analytical observational study designs (i.e., case-control, cohort, case-cohort, nested case-control, or cross-sectional studies) investigating the association between prenatal cannabis use (exposure of interest) and congenital birth defects (i.e., cardiovascular/heart, gastrointestinal, genitourinary, central nervous system, musculoskeletal, or oral cleft defects) (outcome of interest) in offspring were included without publication year restrictions. Importantly, our systematic review encompassed a diverse range of studies, not exclusively focusing on cannabis-only use during pregnancy. We considered a broad spectrum of research, which incorporating cannabis use during pregnancy among various substances and illicit drug uses, accounting prenatal cannabis exposure as a single factor. We assessed the potential impacts of cannabis on structural birth defects as an independent factor, adjusting for other illicit drugs or substances.

Inclusion criteria comprised studies meeting the following conditions: i) any observational study; ii) conducted based on maternal cannabis use during pregnancy; iii) reported the appropriate effect measures such as odds ratio (OR), relative risk (RR), or provided data to calculate effect estimates; iv) written in English language; and v) included a control group (healthy babies). Animal studies, case reports, commentaries, reviews, letters to editor, and conference proceedings were excluded.

2.3. Data sources and search strategies

We comprehensively searched of PubMed/Medline, Scopus, EMBASE, Web of Science, ProQuest, and PsycINFO) and grey literature to include relevant articles from inception of the databases to 25 January 2024. Additionally, we conducted extended reference searching through snowballing to include potentially relevant studies.

The search strategies involved combining Medical Subject Heading (MeSH) terms and free-text search terms using various Boolean operators. For example, PubMed search: ((“cannabis”[MeSH Terms] OR "cannabinoids"[MeSH Terms] OR "marijuana smoking"[MeSH Terms] OR "marijuana abuse"[MeSH Terms] OR (cannabis OR cannabinoid* OR cannabinol* OR dronabinol* OR tetrahydrocannabinol* OR THC OR cannabidiol* OR "cannabis sativa" OR "cannabis indica" OR "cannabis use*" OR "cannabis use disorder*" OR "cannabis abuse*" OR "cannabis dependence" OR "cannabis exposure" OR "substance use*" OR "substance abuse*" OR "substance dependence* OR "substance use disorder" OR marijuana OR Hashish* OR shisha* OR "marijuana use*" OR "marijuana abuse" OR "marijuana dependence" OR "marijuana smoking" OR Ganja) AND ("Congenital Abnormalities"[MeSH Terms] OR Heart Defects, Congenital[Mesh Terms] OR "pregnancy outcome"[MeSH Terms] OR “neural tube defects”[Mesh Terms] OR ("congenital anomaly" OR "birth defect*" OR "birth defects" OR "congenital abnormalit*" OR "congenital abnormalities" OR "congenital defects" OR "Fetal Malformations" OR "Fetal Anomalies" OR "fetal defects" OR "pregnancy outcome*" OR "adverse pregnancy outcome" OR "adverse birth outcomes" OR "adverse perinatal outcome" OR "pregnancy outcome" OR "fetal outcome" OR "obstetric outcome" OR "gestational outcomes" OR "birth outcomes")).

2.4. Data abstraction

Two reviewers (A.W.T and B.S.T) extracted the data from eligible studies. The data extraction was done in accordance with the PRISMA guidelines (Page et al., 2021) and our eligibility criteria. The data abstraction form included: General information (title of the article, first author, publication year, geographical location/study setting), study characteristics (design, follow-up, sample size, inclusions/exclusions), participants’ characteristics (prenatal exposure period, ascertainment of exposure and outcome, matching factors, body system affected) and results [(i.e., number of participants, study population, reported appropriate effect measures such as ORs, RRs, HRs, or raw data provided for calculation of effect estimates, and adjustment for at least one potential confounder (if applicable)]. In cases where certain variables or data were missing, we proactively reached out to the corresponding authors to request the necessary information for hand-calculating the effect estimates of each study.

2.5. Study quality assessment

We assessed the methodological quality of the included studies using an appropriate tool for observational studies; the Newcastle Ottawa Quality Assessment Scale (NOS) (Wells et al., 2011). Three independent reviewers conducted the methodological quality assessment (A.W.T, Y. D, and B.S.T) to minimize possible reviewer bias, and the disagreements were resolved by discussion. The NOS had three standard grading categories: high quality (scored 7–9), moderate quality (scored 4–6), and low quality (scored 0–3) (McPheeters et al., 2012). These scores corresponded with three broad criteria: 1) selection of the study groups (four items); 2) comparability between groups (one item); and 3) ascertainment of outcome and exposure variables (three items), which applied for case control and cohort study designs separately. For each item in selection and ascertainment of outcome/exposure items, we awarded a maximum of one star except items in comparability between the group which was awarded a maximum of two stars.

2.6. Data synthesis and analysis

This cumulative meta-analysis conducted using Stata version 17. The final cumulative meta-analysis included studies that provided an effect estimate such as odds ratios (OR), relative risks (RR), or had data necessary for computing these estimates. To assess how the pooled estimate and its precision changed over time, studies were arranged in ascending order based on their year of publication. Subsequently, the cumulative meta-analysis was iteratively performed, gradually incorporating each newly published study over time. In cases where studies reported multiple estimates, we considered the effect estimate (OR/RR) with the most extensive confounding factor adjustment for final analysis. If studies in the cumulative meta-analysis reported various outcomes such as cardiovascular, gastrointestinal, genitourinary, musculoskeletal, central nervous system defects, or any birth defects (unclassified), the estimate for each outcome was included in the cumulative meta-analysis.

For studies reported estimates for individual trimesters of exposure but not for the entire pregnancy period, we took the estimates for first-trimester prenatal exposure to cannabis in the final analysis. Due to substantial heterogeneity across studies, an inverse variance weighted random-effects cumulative meta-analysis model was employed to combine studies and estimate the association between prenatal cannabis exposure and birth defects (Borenstein et al., 2010).

We considered odds ratios as approximations of relative risks based on the assumption commonly employed in epidemiology, specifically when the outcome of interest is rare and the incidence of an outcome of interest (birth defects) in the study population is lower than <10% (Zhang and Yu, 1998; Kim, 2017; Viera, 2008; Alavi et al., 2020). Additionally, since most of the studies included in our cumulative meta-analysis reported risk estimates using ORs, we reported all of the risk estimates as ORs with the corresponding 95% confidence interval.

To assess the heterogeneity among the included studies, we applied the Cochran's Q statistic test [26] and I^2 statistic test (Higgins and Thompson, 2002a), which has values 25, 50, and 75% to represent low, moderate, and high heterogeneity, respectively (Higgins and Thompson, 2002b; Higgins et al., 2003). A random-effect meta-analysis with cumulative meta-analysis was carried out to account for the potential heterogeneity among studies because this model is more conservative compared to the fixed-effects model (Borenstein et al., 2010). We conducted a subgroup analysis by confounders/covariates adjustment (adjusted/unadjusted), study designs (case-control/cohort), and quality scores (high/ moderate) to identify the source of heterogeneity across included studies. We also did a sensitivity analysis to evaluate the stability of the results by removing a study with a larger relative weight for few of our outcome variables (Patsopoulos et al., 2008). Moreover, meta-regression analysis was conducted to detect heterogeneity between the studies included in our meta-analysis (Ferrari et al., 2013). Finally, publication bias was investigated using the visual inspection of funnel plots (Liu, 2011) and Egger's test (Egger et al., 1997).

3. Results

3.1. Selection process of the included studies

As shown in Fig. 1, our systematic electronic search retrieved 11,756 articles. The screening was done using Rayyan online screening tool. After removing duplicates and screening for title/abstracts, 11,511 articles were excluded as they did not satisfy the eligibility criteria. The remaining 245 articles were selected for full text reading. Meanwhile, eight articles were retrieved through other sources (extended referencing). Finally, thirty-six studies met the inclusion criteria and were included in this cumulative meta-analysis.

3.2. Characteristics of the included studies

Table 1 summarises the key characteristics of the studies included in this systematic review and meta-analysis. The included studies comprise a total of 230,816 cases and 19,049,013 controls. Of the included studies, eighteen were case control (50%) and the remaining were cohort studies. While the majority of these studies conducted in the United States (n = 25) (Torfs et al., 1994; van Gelder et al., 2014; Chawla, 2018; Cornelius et al., 1995; Siega-Riz et al., 2020; Forrester and Merz, 2006; Patel and Burns, 2013; Williams et al., 2004; Kharbanda et al., 2020; Shaw et al., 1996; Wilson et al., 1998; Linn et al., 1983; Mac Bird et al., 2009; Bandoli et al., 2021; Coleman-Cowger et al., 2018; Downing et al., 2019; Ewing et al., 1997; Adams et al., 1989; Correa-Villaseñor et al., 1994; Petrangelo et al., 2019; Warshak et al., 2015; Werler et al., 2014; Witter and Niebyl, 1990; Zuckerman et al., 1989; Steinberger et al., 2002), and the remaining studies were conducted; five in Canada (Koto et al., 2022; Luke et al., 2022; Bourque et al., 2021; Weinsheimer and Yanchar, 2008; Skarsgard et al., 2015), three in the United Kingdom (n = 3) (David et al., 2014; Bandy et al., 2018; Luke et al., 2020) (Table 1), one in Norway (Gabrhelík et al., 2020), one in Spain (Ortigosa et al., 2012) and one in France (Bouquet et al., 2023). The included studies were published between 1983 (Linn et al., 1983) and 2023 (Bouquet et al., 2023). Further these studies were stratified based on the defects of specific body systems; cardiovascular (n = 26), gastrointestinal (n = 16), central nervous system (n = 9), genitourinary (n = 7), orofacial defects (n = 6), musculoskeletal defects (n = 4), and any (unclassified) birth defects (n = 18) (*Table 2*).

3.3. Quality assessment of studies included in meta-analysis

Of the studies included in the quantitative analysis ($n = 36$); 66.7.0% of the included studies scored high quality scores (WHO, 2023; WHO, CDC, 2020; Hackshaw et al., 2011) and the remaining 33.3%scored moderate quality scores (Singh et al., 2020; WHO, 2010; WHO, 2020) based on NOS quality rating scales. No studies scored low NOS rating scale (NOS: 0-3 scores) *(Table S1)*.

3.4. Confounding variables

Of the total studies included in this meta-analysis, 61.1% adjusted for at least one potential confounders, with the most common including tobacco smoking during pregnancy (n = 13), alcohol consumption in pregnancy (n = 6), other illicit drug use (n = 7), maternal body mass index (BMI) (n = 9), and obstetric complications such as diabetes mellitus & hypertension (n = 11). However, other significant confounding variables including maternal mental health problems, socioeconomic status (SES), and child related factors like child sex were not well accounted in the included studies *(Table S2)*.

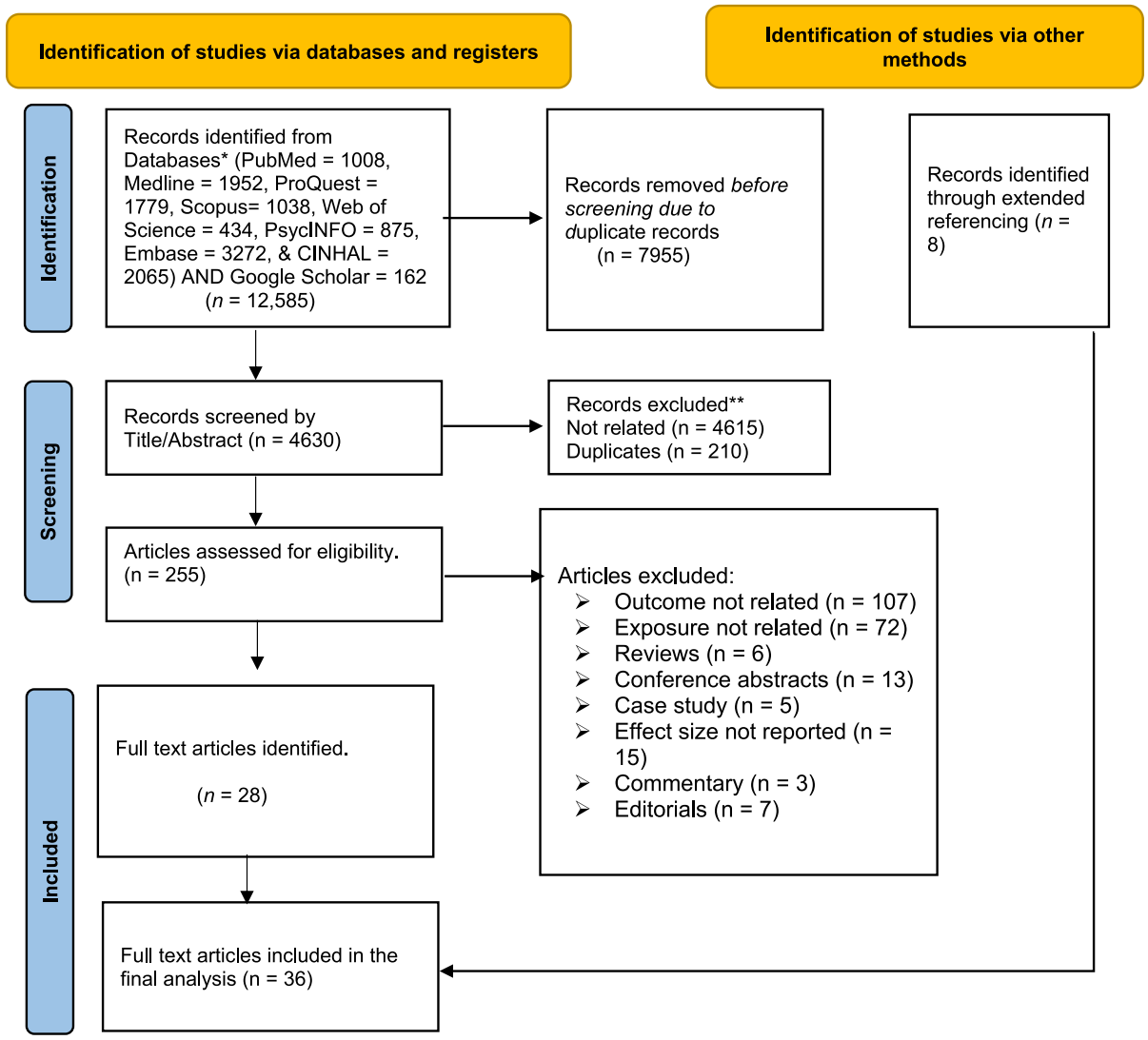

Fig. 1. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA-2020) flow chart to screen the studies to be included in the review.

3.5. Prenatal cannabis uses and risk of congenital birth defects

Our inverse variance weighted random effect meta-analysis found that offspring who were prenatally exposed to cannabis had a 25% increased risk of any birth defects [OR = 1.25: 95 % CI 1.12 – 1.41, I^2 = 76.35%, p < 0.01] compared to non-exposed offspring counterparts (Suppl. Fig. 1). The cumulative meta-analysis of odds ratios (ORs) is quite similar and consistently supported the conventional meta-analysis findings (Fig. 2). When we conducted the meta-analyses by specific body systems, we found increased risks of the gastrointestinal [OR =2.42: 95 % CI 1.61 – 3.64], genitourinary [OR = 2.39: 95 % CI 1.11 – 5.17], central nervous system [OR = 2.87: 95 % CI 1.51 – 5.46], and cardiovascular [OR =2.35: 95 % CI 1.63 – 3.39] defects in offspring. However, we found null associations for musculoskeletal defects [OR = 1.01: 95% CI 0.75 – 1.36] and orofacial [OR = 2.13: 95 % CI 0.93 – 4.84] defects (Table 2).

3.6. Subgroup and sensitivity analyses

In this study, we found substantially high heterogeneity for few outcomes. For example, we noticed high heterogeneity among studies included for cardiac defects (I^2 = 99.03%), which needs handling with different heterogeneity accounting techniques (Fig. 3).

In the subgroup analysis, the cohort studies reported an increased risk of cardiovascular defects compared to case control studies, which is higher than the overall effect estimates as well. Similarly, those studies that did not adjust for at least one potential confounder had a higher risk of birth defects in offspring than studies that accounted for potential confounders. Furthermore, studies with high quality NOS scores indicated a slightly higher risk of birth defects in offspring compared to studies with moderate rating scales (Table 3).

3.7. Leave-one-out sensitivity analysis

We conducted a leave-one-out sensitivity analysis by omitting each study one a time to see the effect of a single study on the overall effect estimates for any birth defects, cardiovascular, CNS, genitourinary and gastro-intestinal defects. However, our estimates were not substantially affected by individual studies (Suppl. Fig. 3).

3.8. Publication bias

In this meta-analysis, we visualized and examined the funnel plots of included studies for gastrointestinal, any defects, CNS, genitourinary, musculoskeletal, and cardiac defects., We found symmetrical plots, and the egger test showed no publication bias (P = 0.1201, 0.4550, 0.0588, 0.1658, 0.239, and 0.0150, respectively). Therefore, inclusion of studies reporting null associations (no observed effects) and small studies in the

Table 1
Summary of studies included in this systematic review and meta-analysis.

Authors: Year	Study design	Study Setting	Confirmation of outcomes	Total sample size	Total cases	Exposure period	The reported associations: Account confounders (any):
Adams et al., 1989	Case-control	USA	medical records	1386	83		Crude associations
Bandoli et al., 2021	Cohort	USA	ICD	3,066,868	81,684	any pregnancy	Adjusted associations
Bandy et al., 2018	Cohort	UK	medical records	1,382	35	any pregnancy	Adjusted
Bouquet et al., 2023	Cohort	France	medical records	669	47	any pregnancy	Adjusted associations
Bourque et al., 2021	Cohort	Canada	medical records	1,000,849	231	any pregnancy	Crude associations
Chawla et al., 2018	Case-control	USA	medical records	33,435	21,942	any pregnancy	Crude associations
Coleman-Cowger et al., 2018	Case-control	USA	medical records	414	36	any pregnancy	Crude associations
Cornelius et al., 1995	Cohort	USA	ICD	294	48	First trimester	Adjusted associations
Correa-Villaseñor et al., 1994	Case-control	USA	medical records	3716	44	any pregnancy	Adjusted associations
David et al., 2014	Case-control	UK	medical records	481	36	Second/third trimester	Crude associations
Downing et al., 2019	Case-control	USA	medical records	11,829	135	any pregnancy	Adjusted associations
Ewing et al., 1997	Case-control	USA	ICD	4,040	491	First trimester	Crude associations
Forrester et al., 2006	Cohort	USA	ICD	316,508	6276	First trimester	Crude associations
Gabrhelík et al., 2020	Cohort	Norway	medical records	10,101	539	any pregnancy	Crude associations
Kharbanda et al., 2020	Cohort	USA	ICD	3,380	55	First trimester	Adjusted associations
Koto et al., 2022	Cohort	Canada	ICD	100,437	5,845	any pregnancy	Adjusted associations
Linn et al., 1983	Case-control	USA	medical records	12,088	336	any pregnancy	Adjusted associations
Luke et al., 2020	Cohort	UK	ICD	3,301	245	any pregnancy	Crude associations
Luke et al., 2022	Cohort	Canada	ICD	1,045,237	6,533	any pregnancy	Adjusted associations
Mac Bird et al., 2009	Case-control	USA	medical records	5620	653	any pregnancy	Adjusted associations
Van Gelder et al., 2014	Case-control	USA	ICD	8,711	14,124	any pregnancy	Adjusted associations
Ortigosa et al., 2012	Cohort	Spain	medical records	101	5	any pregnancy	Crude associations
Patel & Burns, 2013	Case-control	USA	medical records	3,572	3377	any pregnancy	Crude associations
Petrangelo et al., 2019	Cohort	USA	ICD	12,581,557	50,058	any pregnancy	Adjusted associations
Shaw et al., 1996	Case-control	USA	medical records	539	49	First trimester	Adjusted associations
Siega-Riz et al., 2020	Cohort	USA	medical records	736,827	34720	Second/third trimester	Adjusted associations
Skarsgard et al., 2015	Case-control	Canada	medical records	5400	692	any pregnancy	Adjusted associations
Steinberger et al., 2002	Case-control	USA	ICD	3620	48	any pregnancy	Crude associations
Torfs et al., 1994	Case-control	USA	medical records	220	110	First trimester	Adjusted associations
Warshak et al., 2015	Cohort	USA	Medical records	6468	230	any pregnancy	Adjusted associations
Weinsheimer & Yanchar, 2008	Cohort	Canada	medical records	4,447	114	any pregnancy	Adjusted associations
Werler et al., 2014	Case-control	USA	ICD	2683	80	First trimester	Adjusted associations
Williams et al., 2004	Case-control	USA	medical records	3,129	122	Second/third trimester	Adjusted associations
Wilson et al., 1998	Case-control	USA	medical records	3,572	4,296	any pregnancy	Crude associations
Witter & Niebyl, 1990	Cohort	USA	Medical records	8,350	387	any pregnancy	Crude associations
Zuckerman et al., 1989	Cohort	USA	Medical records	1,664	18	any pregnancy	Crude associations
			Grand Total	**19,049,013**	**230,816**		

Note: USA: United States of America, UK- United Kingdom, ICD- international classifications of disease, any pregnancy- cannabis exposure time was not specified into either first, second or third trimesters.

analysis did not introduce a bias that would compromise the overall findings.

4. Discussion

Prenatal cannabis exposure has become a prominent public health concern due to the increasing prevalence of cannabis use during pregnancy. Understanding the potential association between prenatal cannabis exposure and the risk of structural birth defects is crucial for guiding clinical practice and formulating evidence-based policies. We conducted this cumulative meta-analysis, incorporating conventional meta-analysis, to provide a comprehensive understanding of the relationship between cannabis use during pregnancy and structural birth defects in offspring. This meta-analysis offers a robust approach to examine the association between prenatal cannabis exposure and birth defects in offspring.

This cumulative meta-analysis found that prenatal exposure to cannabis was associated with an increased risk of any birth defects, and specifically defects of the gastrointestinal, central nervous system, genitourinary, and cardiovascular systems in exposed offspring.

The existing evidence from animal models links prenatal cannabis exposure with multifaceted adverse effects on maternal, gestational,

Table 2
The pooled effect estimates of prenatal cannabis use and risk of congenital birth defects sub-grouped by specific body systems defects.

Major Congenital defects	Number of studies	Number of total cases	Pooled OR	95% CI	Heterogeneity (I^2, p-value)	Publication bias (Egger's test)
Cardiovascular/heart defects	**26**	**30, 157**	**2.35**	**1.63 – 3.39**	**I^2 = 99.03%, p < 0.001**	**P < 0.0150**
Any cardiac defects (CHD)	3	-	1.16	1.01 – 1.45	I^2 = 63.13%, p = 0.07	
Ebstein's anomaly	2	-	2.46	1.24 – 4.84	I^2 = 34.12%, p = 0.22	
Septal defects (SD)	8	-	1.89	1.05 – 3.42	I^2 = 99.12%, p < 0.001	
Hypoplastic left heart syndrome (HLHS)	2	-	3.56	0.82 – 6.41	I^2 = 98.81%, p < 0.001	
Tetralogy of Fallot (TOF)	2	-	3.25	0.60 – 27.28	I^2 = 98.84%, p < 0.001	
Valve stenosis	4	-	5.02	2.84 – 8.89	I^2 = 95.99%, p < 0.001	
Coarctaion of aorta	2	-	2.50	0.60 – 10.44	I^2 = 95.44%, p < 0.001	
Conotruncal	1		1.08	0.53 – 2.21	N/A	
Transposition of great arteries	2	-	1.45	0.42 – 5.00	I^2 = 81.61%, p < 0.001	
Gastrointestinal and abdominal wall defects	**16**	**17,856**	**2.42**	**1.61 – 3.64**	**I^2 = 90.95%, p < 0.001**	**P = 0.1201**
Gastroschisis	7	-	2.93	1.50 – 5.74	I^2 = 93.72%, p < 0.001	
Diaphragmatic hernia	1	-	1.4	0.89 – 2.2	N/A	
Oesophageal atresia	1	-	1.4	0.82 – 2.4	N/A	
Intestinal atresia	2	-	2.96	0.46 - 18.86	I^2 = 85.71%, p < 0.01	
Ano-rectal atresia	2	-	2.25	0.26 – 19.3	I^2 = 91.7%, p < 0.001	
Omphalocele	1	-	1.01	0.43 – 2.36	N/A	
Pyloric stenosis	1	-	7.63	3.16 - `8.43	N/A	
Upper alimentary tract	1	-	2.07	0.59 – 7.27	N/A	
Central nervous system	**9**	**10,109**	**2.87**	**1.51 – 5.46**	**I^2 = 91.36%, p < 0.001**	**P = 0.0588**
Anencephaly	1	-	2.2	1.31 – 3.7	N/A	
Encephalocele	1	-	9.06	5.99 – 16.65	N/A	
Hydrocephaly	2	-	6.61	2.58 – 16.94	I^2 = 32.19%, p = 0.22	
Neural tube defects	2	-	0.99	0.62 – 1.58	I^2 = 70.04%, p = 0.07	
Microcephaly	1	-	9.53	4.74 – 19.16	N/A	
Spinal bifida	2	-	1.42	0.4 – 5.09	I^2 = 60.86%, p = 0.11	
Genitourinary defects	**7**	**2,951**	**2.39**	**1.11 – 5.17**	**I^2 = 78.79%, p < 0.01**	**P = 0.1658**
Hypospadias	3	-	1.06	0.66 – 1.71	N/A	
Cystic kidney	1	-	2.67	0.37 – 19.15	N/A	
Genital defect	1	-	5.99	1.01 – 35.7	N/A	
Obstructive Genito-urinary	1	-	5.96	2.83 – 12.54	N/A	
Renal genesis	1	-	5.3	1.31 – 21.39	N/A	
Oro-facial defects	**6**	**11,585**	**2.13**	**0.93 – 4.84**	**I^2 = 99.24%, p < 0.001**	**P = 0.001**
Cleft lip + palate	3	-	1.96	0.48 – 8.02	I^2 = 99.29%, p < 0.001	
Cleft palate	2	-	3.26	0.33 – 31.9	I^2 = 99.19%, p < 0.001	
Eye	1	-	1.1	0.71 – 1.71	N/A	
Musckuloskeletal system defects	**4**	**1,317**	**1.01**	**0.75 – 1.36**	**I^2 = 0%, p = 0.58**	**P = 0.239**
Craniosynostosis	1	-	0.8	0.49 – 1.3	N/A	
Clubfoot	2	-	1.33	0.79 – 2.26	I^2 = 0%, p = 0.96	
Lib reduction deficit	1	-	1.01	0.6 – 1.71	N/A	
Any birth defects (unspecified birth defects)	18	156,841	1.25	**1.12 – 1.41**	I^2 = 76.35%, p < 0.01	P = 0.4550

Note: OR- Odds Ratio, N/A- not applicable, any birth defects- unspecified or unclassified major birth defects

placental, and foetal outcomes. However, the mechanisms are not well understood. The suggested mechanisms could be explained with the impaired placental function and development, foetal in-utero growth, foetal structural morphology at birth, and offspring neurodevelopment (Olyaei et al., 2022; Schneider, 2009; Carty et al., 2018).

The biological mechanisms linking prenatal cannabis exposure and congenital birth defects in human offspring remains to be elucidated. The Δ9-tetrahydrocannabinol- THC, the psychoactive ingredient and most potent form of cannabis, can readily pass through the placental and blood-brain barrier, providing a mechanism for prenatal cannabis exposure (PCE) that affects in-utero foetal development (Blackard and Tennes, 1984; Little and VanBeveren, 1996; Ma et al., 2003). This psychoactive ingredient of cannabis may impair placental blood circulation and embryonic foetal development (El Marroun et al., 2010; Natale et al., 2020). Thus, it is plausible that exposure to cannabis in-utero can be associated with an increased risk of birth defects, which may include one or more of the body systems in exposed offspring (Pallotto and Kilbride, 2006; Toufaily et al., 2018; Wallenstein et al., 2012; Fant et al., 2014). Additional insights from a study conducted by Ortigosa et al. suggest that prenatal drug use may induce alterations in the fetoplacental vasculature. These alterations have the potential to disturb blood flow, which, in turn, might account for the observed adverse effects in neonates exposed to drugs during fetal life (Ortigosa et al., 2012). This mechanism underscores the importance of exploring the potential link between prenatal cannabis use and the heightened risk of birth defects, as alterations in fetoplacental vasculature could contribute to adverse outcomes in newborns.

Our finding is supported by a 2023 study conducted by Dave et al that reported positive pooled unadjusted associations between in-utero cannabis exposure and a range of structural birth defects that were usually attenuated after the inclusion of only adjusted estimates (Delker et al., 2023). Further the findings of this meta-analysis are consistent

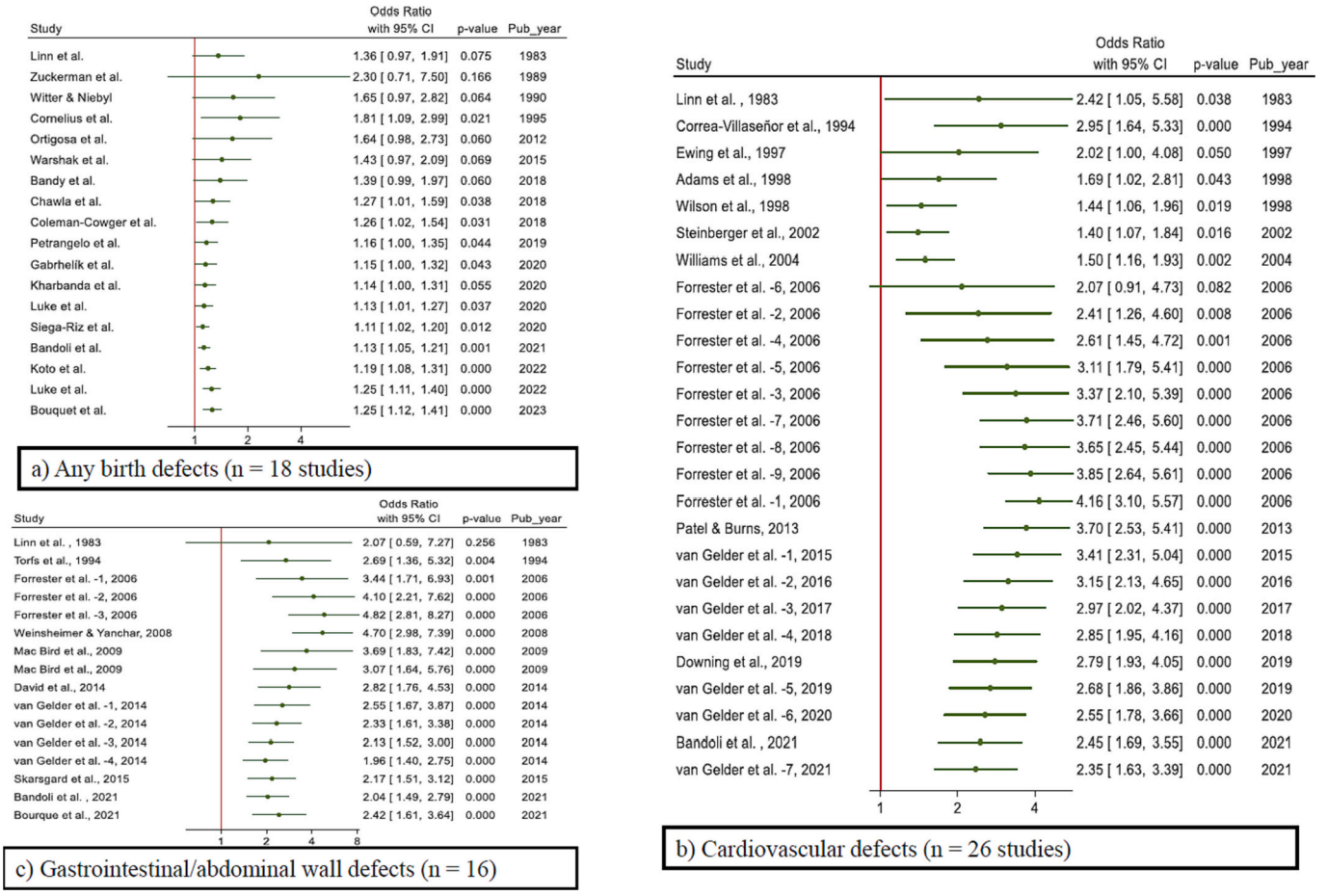

Fig. 2. Converging cumulative odds ratio (COR) with each successive publication on the association between prenatal cannabis exposure and (a) any birth defects; (b) cardiac defects; and (c) gastrointestinal defects. All estimates were carried out based on random-effects estimator.

with the finding of a scoping review study by Richardson and colleagues (2019) that reviewed the teratological effect of prenatal cannabis exposure from a wide range of observational longitudinal studies (Richardson et al., 2016). Additionally, the findings of our study are supported by another review study by Huizink (2014) that demonstrates the impact of prenatal cannabis use on neonatal health outcomes, including congenital defects in offspring (Huizink, 2014). Moreover, our meta-analyses findings supported the American College of Obstetricians and Gynaecologists (ACOG) recommendation that explained pregnant mothers should avoid cannabis use during the prenatal period to reduce risk of adverse birth outcomes, including congenital birth defects (ACOG, 2017).

Our subgroup analysis revealed an increased risk of congenital birth defects in both cohort and case control study designs, but cohort studies showed a higher risk of birth defects than case control studies. It has been argued that longitudinal studies can better establish temporality between exposure and an outcome of interest as opposed to case control studies. This may explain the increased risk reported in the cohort studies subgroup analysis (Shimonovich et al., 2021; Vineis, 2003).

Furthermore, our subgroup analysis also indicated the risk of birth defects in offspring was higher in studies that did not account for at least one important confounder such as prenatal tobacco smoking than their counterparts. This could be explained by numerous confounding factors such as tobacco and alcohol use that can independently contribute to congenital birth defects, making it difficult to understand the specific impact of cannabis (Koto et al., 2022; Hackshaw et al., 2011). Additionally, women who use cannabis during pregnancy may have different socioeconomic backgrounds and/or access to healthcare, which can also contribute to adverse birth outcomes, including congenital birth defects. Besides, among the studies that did not adjust for confounders, more than three-fourths were case-control studies, in contrast to those studies that took into account influential confounders. Thus, the association between prenatal cannabis exposure and the risk of birth defects might be influenced by these uncontrolled residual confounders and maternal factors in these studies.

4.1. *The strengths and limitations of the study*

This meta-analysis offers a robust approach to examine the association between prenatal cannabis exposure and congenital birth defects and has several strengths. Firstly, the notable strength of the current meta-analysis lies in its application of cumulative meta-analyses, distinguishing it from prior study predominantly reliant on conventional meta-analysis to consolidate the evidence on the subject area. Secondly, the methodological quality of included studies was assessed using a standard and well-accepted methodological quality assessment tool, NOS, with all included studies found to be of good quality. Thirdly, we carried out subgroup analyses to explore the source of heterogeneity and sensitivity analysis to identify highly influential studies on the overall effect estimate. Fourth, we also conducted meta-regression to identify potential sources of heterogeneity.

The current review also has limitations. We have synthesized data from observational studies with varying samples and methodologies. Therefore, we observed considerable heterogeneity between included studies in the association between prenatal cannabis exposure and birth defects. Few important studies may have been excluded during screening and extraction if the studies did not report the required effect size estimates or provided the relevant data to calculate the effect

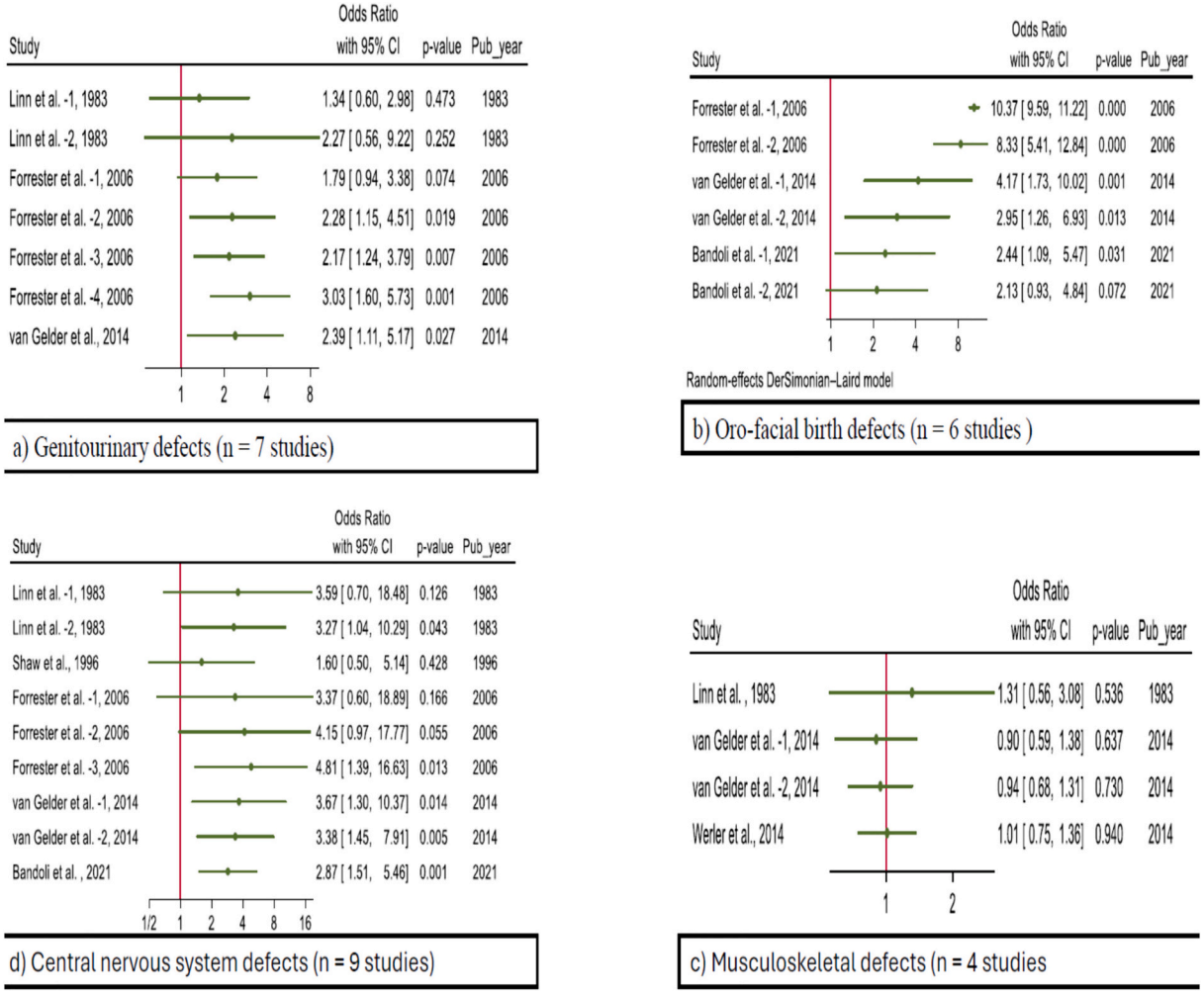

Fig. 3. Converging cumulative odds ratio (COR) with each successive publication to examine prenatal cannabis exposure and risk of; (a) genitourinary tract defects; (b) orofacial defects; (c) central nervous defects; and (d) musculoskeletal defects. All estimates were carried out based on random-effects estimator.

estimates. Further we also acknowledge the limitations associated with the absence of detailed information on dosing, frequency, and timing of cannabis use in the included studies. Additionally, we recognize the variability in study methodologies, where not all investigations incorporated biological confirmation of cannabis and other substance use. Furthermore, we noted that the level of adjustment for confounders was inconsistent in these studies, suggesting our results might be biased by residual confounding. Hence, caution should be considered when interpreting and generalizing the findings of this study.

5. Conclusion

We undertook a comprehensive systematic review and meta-analysis of prenatal cannabis use and the risk of congenital birth defects in offspring. Our findings suggest that that maternal prenatal cannabis use may increase the risk of different forms of birth defects, specifically defects of the gastrointestinal, central nervous system, genitourinary and cardiovascular system in offspring. The findings underscore the significance of implementing preventive strategies, including enhanced preconception counselling, to address cannabis use during pregnancy and mitigate the risk of birth defects in offspring. Further studies are needed to confirm and assess the mechanisms behind these associations.

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Authors contribution

A.W.T conceived the hypothesis, developed the methodology, identified all potential studies, extracted the data, assessed quality of included studies, conducted a meta-analysis, and wrote the first draft of the manuscript and revised the subsequent drafts of the manuscript. G.A, Y.D, and B.S.T assessed the methodological quality of the included studies and critically reviewed the manuscript for important intellectual content. G.A, K.B, B.A.D, and R.A supervised and critically reviewed subsequent drafts of the manuscript. All authors read and approved the final version of the manuscript.

CRediT authorship contribution statement

Abay Woday Tadesse: Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Data curation, Conceptualization. **Getinet Ayano:** Writing – review & editing, Supervision, Methodology. **Berihun Assefa Dachew:** Writing – review & editing, Supervision. **Biruk Shalmeno Tusa:** Methodology. **Yitayish Damtie:** Methodology. **Kim Betts:** Writing – review & editing, Supervision. **Rosa Alati:** Writing – review & editing, Supervision.

Table 3
Subgroup analysis to see the variation in the overall effects of prenatal cannabis exposure to a range of birth defects in offspring.

Sub-grouped (stratified) by:	Categories (if any)	CVS defects		GI defects		CNS defects		Any defects (unclassified defects)	
		N0. of studies	OR (95% CI)	N0. of studies	OR (95% CI)	N0. of studies	OR (95% CI)	N0. of studies	OR (95% CI)
Reported effect estimates	Adjusted	11	1.13 (0.93, 1.37)	10	1.57 (1.14, 2.17)	4	1.14 (0.79, 1.65)	12	1.29 (1.11, 1.50)
	Crude	15	3.88 (2.6, 5.79)	6	5.38 (2.46, 11.77)	5	8.67 (5.4, 13.93)	6	1.17 (0.96, 1.43)
Study design	Cohort	10	6.15 (4.31, 8.78)	6	5.35 (1.73, 16.52)	4	6.32 (1.44, 27.69)	16	1.27 (1.11, 1.46)
	Case-control	16	1.18 (1.03, 1.35	10	1.65 (2.35)	5	1.37 (0.77, 2.44)	2	1.15 (1.03, 1.28
Studies adjusted for maternal smoking during pregnancy	Yes	8	0.98 (0.88, 1.11)	7	1.33 (1.05, 1.68)	4	1.14 (0.79, 1.65)	8	1.24 (1.07, 1.43)
	No	18	3.57 (2.47, 5.17)	9	3.65 (1.97, 6.76))	5	8.67 (5.4, 13.93)	10	1.28 (1.04, 1.57)
Studies adjusted for maternal alcohol drinking	Yes	8	0.98 (0.88, 1.11)	5	1.24 (1.07, 1.44)	3	1.29 (0.86, 1.93)	5	1.33 (1.07, 1.66)
	No	18	3.57 (2.47, 5.17)	11	3.6 (2.09, 6.18)	6	4.81 (1.39, 16.63)	13	1.22 (1.05, 1.42)
Cannabis exposure time during pregnancy	1st trimester	10	6.43 (4.86, 8.50)	4	5.49 (3.25, 9.25)	4	5.66 (1.14, 28.0)	2	1.38 (0.26, 7.37)
	2nd/3rd trimester	1	1.9 (1.29, 2.8)	1	2.33 (1.67)	Nill	-	1	1.09 (1.01, 1.18)
	Any pregnancy	15	1.11 (0.98, 1.25)	11	1.88 (1.14, 3.11)	5	1.42 (0.96, 2.10)	15	1.28 (1.12, 1.46)
NOS quality score	High (7-9 scores)	20	2.68 (1.89, 3.81)	14	2.41 (1.55, 3.74)	7	2.81 (1.38, 5.72)	12	1.18 (1.05, 1.33)
	Moderate (4-6 scores)	6	1.31 (1.63, 3.39)	2	2.69 (1.36, 5.32)	2	3.27 (1.04, 10.29)	6	1.42 (1.06, 1.89)

Key: OR- Odds Ratio, NOS- Newcastle Ottawa Scale, CI- confidence intervals, any pregnancy- indicates cannabis exposure during pregnancy with no specification to trimesters.

Declaration of competing interest

All authors have no conflicts of interest to disclose.

Data availability

Data will be made available on request.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ntt.2024.107340.

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