Journal of Hazardous Materials 486 (2025) 137028

Contents lists available at ScienceDirect

Journal of Hazardous Materials

journal homepage: www.elsevier.com/locate/jhazmat

Review

Associations between vaping during pregnancy and perinatal outcomes: A systematic review and meta-analysis

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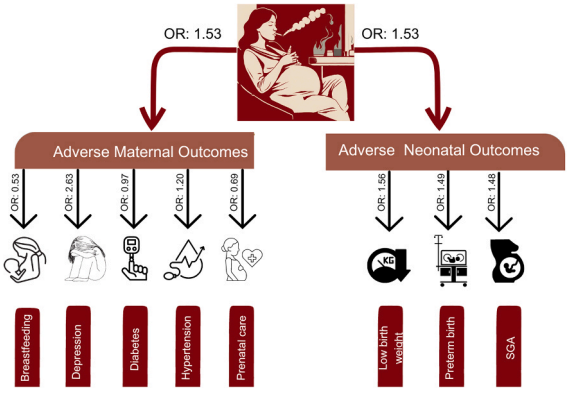
HIGHLIGHTS

- First meta-analysis linking vaping during pregnancy and adverse perinatal outcomes.
- Vaping during pregnancy increases the risk of pregnancy and perinatal outcomes.
- Addressing awareness about vaping for health and environment is urgently needed.

GRAPHICAL ABSTRACT



ARTICLE INFO

Keywords:
Vaping
Electronic cigarettes
Pregnancy
Prenatal care
Perinatal outcomes

ABSTRACT

Despite numerous studies linking prenatal vaping to adverse perinatal outcomes, a systematic assessment for critical comparison remains absent. To investigate these associations, we conducted a systematic search of studies assessing perinatal outcomes in mothers and/or neonates exposed to vaping during pregnancy compared to those in women without prenatal vaping exposure through MEDLINE, EMBASE, Scopus, Web of Science, Cochrane Library, PROSPERO, and Google Scholar until July 5, 2024. We performed inverse-variance random-effects meta-analyses for maternal and neonatal outcomes of 23 studies with a total of 924,376 participants with

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https://doi.org/10.1016/j.jhazmat.2024.137028
Received 17 September 2024; Received in revised form 2 December 2024; Accepted 25 December 2024
Available online 26 December 2024

7552 reporting vaping-only use during pregnancy. Prenatal vaping was associated with 53 % higher odds of an adverse maternal outcome (OR: 1.53; 95 % CI: 1.27–1.85; $I^2 = 80$ %), particularly with decreased breastfeeding (OR: 0.53; 95 % CI: 0.38–0.72; $I^2 = 45$ %) and reduced prevalence of adequate prenatal care (OR: 0.69; 95 % CI: 0.56–0.86; $I^2 = 82$ %). Prenatal vaping was also associated with a similarly 53 % higher odds of an adverse neonatal outcome (OR: 1.53; 95 % CI: 1.34–1.76; $I^2 = 45$ %), such as low birth weight (OR: 1.56; 95 % CI: 1.28–1.93; I^2: 15 %), preterm birth (OR: 1.49; 955 CI: 1.27–1.76; I^2: 0 %), and small for gestational age (OR: 1.48; 955 CI: 1.16–1.89; I^2: 70 %). This is the first comprehensive systematic review and meta-analysis demonstrating vaping during pregnancy as a risk factor for increased odds of both maternal and neonatal outcomes and underscores the urgency to address awareness and regulations of vaping and its potential harms to both humans and the environment.
Registration: PROSPERO CRD42023446266.

1. Introduction

Vaping, or the use of electronic cigarettes (e-cigarettes), has emerged as an alternative to traditional cigarette smoking in the past two decades. Although initially touted as a safe alternative to smoking that could be used as a smoking cessation tool [1], vaping has now been implicated in a host of pulmonary conditions. The acute rise in prevalence of such conditions, initially referred to as vaping-associated pulmonary illness (VAPI) and now known as e-cigarette or vaping use-associated lung injury (EVALI), is starting to be realized as an increasing healthcare burden [2,3]. E-cigarette aerosols contain varying levels of nicotine, volatile organic compounds (VOCs), heavy metals (e.g., nickel, tin, lead), and flavorings (e.g., diacetyl) known to damage the lungs and lead to other systemic harms [4,5]. More recent reports have demonstrated possible cardiovascular [6–8], cerebrovascular [9], and systemic [10] effects from vaping. Concerningly, far less is known about the extent of these systemic impacts and their long-term consequences compared to the more acute pulmonary conditions popularized by EVALI. For instance, the European Association of Preventive Cardiology (EAPC) has stated that although e-cigarettes significantly impact cardiovascular function, there is not enough evidence to appreciate the long-term direct cardiovascular effects of e-cigarettes [11]. Intriguingly, the recency of vaping, the sudden increase of its use worldwide, evidence of its acute life-threatening potential, and uncertainty towards the extent of its systemic effects have not attracted adequate awareness campaigns, regulatory policies, and statutory warnings on packaging [12] when compared to those in place for tobacco products [13,14].

The influence of vaping during pregnancy has gained increasing attention due to its prevalence in the general population, emerging research reports suggesting its adverse effects, and the suggested use of vaping as a tobacco cessation technique during pregnancy. Prenatal vaping raises numerous concerns for both maternal and fetal health due to the potentially addictive, carcinogenic, and teratogenic nature of its components. As maternal and fetal perinatal outcomes continue to be concerning global health issues [15], it is critical to consider how increasing use of vaping products could be implicated in such matters [16]. In the past decade, large population-based databases such as the Pregnancy Risk Assessment Monitoring System (PRAMS) and Population Assessment of Tobacco and Health (PATH) studies have contributed significant epidemiological evidence to facilitate evidence-based investigations towards these issues [17–20]. For example, PRAMS is a joint surveillance project in the United States that uses birth certificates and multimodal surveys to retrospectively collect information on maternal characteristics and perinatal outcomes from before to shortly after (2–6 months) pregnancy. PRAMS data represent approximately 83 % of national births and since 2016 has included questions on vaping frequency at various perinatal time points [21]. Although several studies have used such data to show that prenatal vaping is associated with adverse perinatal outcomes, a systematic and comprehensive assessment of evidence on this topic that would allow for a critical comparison of such outcomes is lacking.

We, therefore, aimed to conduct a systematic review and meta-analysis to evaluate the associations between vaping during pregnancy and both maternal and neonatal outcomes. We also aimed to determine the effects of vaping on specific maternal (e.g., gestational diabetes and hypertension) and neonatal conditions (e.g., birthweight and preterm birth).

2. Methods

2.1. Study design

This systematic review and meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [22]. A PRISMA checklist is included in the supplemental content (**PRISMA 2020 Checklist**). The study protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO) on July 28, 2023 (CRD42023446266).

2.2. Study selection

Eligibility criteria for this study were informed through the population, exposure, comparison, outcome, and study design (PECOS) framework [22]. We included studies that compared adverse perinatal outcomes in mothers and/or neonates between women who were exposed to vaping during pregnancy versus those who were not exposed to vaping or cigarette smoking (controls/nonusers). Studies that did not isolate vaping exposure from cigarette use (i.e., only reporting dual users) were excluded. Adverse perinatal outcomes were defined as adverse maternal or neonatal outcomes previously discussed in the literature [23,24] and occurring during pregnancy, birth, or the initial postpartum period (<6 months after birth). We included primary studies of any design (except case studies) published in peer-reviewed journals. We did not limit studies by country, date, language, or population. Studies not in English were translated through Google Translate (Google, Mountain View, CA, United States) to assess their eligibility. Secondary research was considered only to identify potential primary studies for inclusion.

We identified search terms through consensus (eTable 1), after which, an author with search experience (A.D.) developed and completed a comprehensive search of MEDLINE (Medical Literature Analysis and Retrieval System Online, or MEDLARS Online), EMBASE (Excerpta Medica dataBASE), Scopus, Web of Science, Cochrane Reviews, Cochrane Protocols, PROSPERO, and Google Scholar to identify studies in an initial search up to June 30, 2023, through University of Alberta library services. No filters or limits were applied to library searches and the complete search strategy is included in the supplementary appendix (eTable 2). Hand searches, bibliographic searches, and contact with study authors were also conducted to identify any further studies. An updated search was completed on July 5, 2024, through the McMaster University Health Sciences Library (eTable 3). Search results were uploaded to the systematic review management software Covidence (Melbourne, VIC, Australia), where duplicate records were removed. Two reviewers (A.D. and S.M.) independently performed the initial screening of titles and abstracts followed by an

independent full-text review of remaining studies for inclusion by these same reviewers. Any disagreements were resolved through consensus or a third reviewer (N.M.).

2.3. Data analysis

Two reviewers (A.D. and S.M.) independently extracted data from included studies into structured Google Sheets (Google, United States). Extracted data items included study (e.g., year, study design, country) and population characteristics (e.g., number of participants, age, cohort, adjusted confounders), vaping exposure (e.g., exposure type, duration, frequency, timing during pregnancy), and adverse perinatal outcomes in vaping and control groups. Only the most recent or complete study was included for investigations with multiple publications. If data were not available for extraction, study authors were contacted. An author with statistical expertise (D.A.) verified all extracted data. Studies meeting eligibility criteria that did not include analyzable outcome data were included in the systematic review but not any meta-analyses.

We performed meta-analyses to assess the associations between prenatal vaping exposure and adverse perinatal outcomes compared to controls. We extracted odds ratios (ORs) and confidence intervals (CIs) from studies with dichotomous outcomes. When ORs and CIs were not presented [19,20,25–36], we calculated them from available data (if a control group was reported) using standard formulae [37]. For continuous outcomes, standardized mean differences (SMDs) were similarly either extracted from studies or calculated if necessary [19,20,38,39]. Different studies used different confounders such as maternal age, race/ethnicity, prenatal alcohol use, family income, prenatal care adequacy, parity/plurality, socioeconomic status, marital status, pre-pregnancy body mass index, gestational weight gain, multivitamin status, along with smoking history and/or frequency while analyzing the data. Therefore, we extracted the most adjusted effect sizes from studies to reduce the influence of confounding variables on associations. Inverse-variance random-effects meta-analyses were first completed for each outcome assessed by multiple ($\geq$2) studies. We then pooled all maternal and neonatal outcomes reported by each study to complete separate overall meta-analyses among studies for both maternal and neonatal outcomes. Separate analyses were completed for dichotomous and continuous outcomes. Sensitivity analyses were completed for overall outcomes with enough studies by excluding studies with a high risk of bias and excluding all but the most recent or largest studies reporting similar outcomes from the same population/cohort. Subgroup analyses were also completed for these outcomes to consider the influence of confounding factors in studies providing both unadjusted and adjusted models with χ^2 tests to assess between-group differences. Heterogeneity was measured through the I^2 statistic, with low, moderate, and high heterogeneity respectively quantified as I^2 values < 50 %, 50–75 %, and > 75 % [40]. Significance was defined as $p < 0.05$. Studies not eligible for meta-analyses were narratively synthesized. All meta-analyses were performed in ReviewManager (RevMan) version 5.4 (Cochrane, London, United Kingdom).

2.4. Quality assessment

Two reviewers (A.D. and S.M.) independently assessed the risk of bias of included studies at the individual study level through the Risk Of Bias In Non-randomized Studies – of Exposures (ROBINS-E) tool [41]. Adequate consideration of confounding factors was assessed with a confounder matrix method [42] informed through models discussed in the included studies [28,43]. ROBINS-E summary figures were created through the Robvis tool (University of Bristol, Bristol, United Kingdom). The certainty of evidence for outcomes was independently assessed for overall outcomes with a sufficient number of studies by the same two reviewers through the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) framework [44]. We additionally assessed publication bias for syntheses of main outcomes through Egger's test [45], Begg's test [46], and visual inspection of funnel plots. Evidence tables were created through GRADEpro (McMaster University, Hamilton, ON, Canada).

3. Results

3.1. Search results

The initial database search identified 914 records, and after removing duplicates and identifying additional records, 493 titles and abstracts were screened for eligibility. After assessing 60 full texts, 25 studies were included in the systematic review and 23 of these were eligible for meta-analyses. Fig. 1 illustrates the complete study selection process. Brief reasons for the exclusion of studies at the full-text review stage are included in the appendix (eTable 4).

3.2. Study characteristics

The 25 studies included in this systematic review and meta-analysis considered 924,376 total participants with 7552 reporting vaping during pregnancy (0.82 % prevalence), were published between 2019 and 2024, and varied in sample size from 67 cases in an Italian study on stillbirths [47] to 242,573 participants in PRAMS Phase 8 [18]. The majority of studies were retrospective cohort in design [17,18,26–34,36,43,48–51], followed by three prospective cohorts [20,25,39], three cross-sectional [19,35,52], and two case-control studies [38,47]. Studies represent data from four countries (Ireland, the Netherlands, the United Kingdom, and the United States); however, most ($n = 20$) were from the United States. Maternal ages for included studies ranged from one adolescent study [18] to an upper age limit of 44 years in three studies [35,39,49]. Summary study characteristics are presented in Table 1.

3.3. Vaping during pregnancy and perinatal outcomes

All studies considered first-hand vaping, while Cardenas et al. was the only one to include a second-hand exposure group [25]. Studies (particularly PRAMS papers) most often assessed outcomes by vaping status during the third trimester, with fewer studies considering use during the first trimester [20], at multiple time points [18,32,39,43], or at any point during pregnancy [17,19,25,35,47,49,52]. Vaping use was infrequently quantified by studies, ranging in frequency from less than once a week to more than once a day when described. Froggatt et al. were the only ones to report nicotine content in vaping devices (3–16 mg) [38] while Lin et al. considered outcomes for different vaping solution flavours [49]. Vaping individuals were frequently pre-pregnancy ever-smokers, with rates above 90 % in some studies [17,20,27]. eTable 5 has further information about exposures assessed by included studies along with the confounders used in the analyses.

Included studies assessed 11 unique maternal and neonatal outcomes described in detail in eTable 6. Neonatal outcomes were reported more frequently than maternal outcomes (21 vs. 18 studies). Breastfeeding, depression, diabetes, hypertension, and prenatal care were the most frequently reported maternal outcomes (eTable 7), and low birth weight (LBW), preterm birth, and small for gestational age (SGA) were most often reported for neonatal outcomes (eTable 8). Outcomes were dichotomous in most studies (24 studies) whereas continuous outcomes were available in five studies. All except six studies reported adjusted models for at least one study outcome (eTable 9).

In the meta-analysis of dichotomous outcomes, vaping during pregnancy was associated with 53 % higher odds of adverse maternal outcomes (OR: 1.53; 95 % CI: 1.27–1.85; $I^2 = 80$ %) and 53 % higher odds of adverse neonatal outcomes (OR: 1.53; 95 % CI: 1.34–1.76; $I^2 = 45$ %) (Fig. 2). Although we found moderate to high heterogeneity in meta-analyses, their funnel plots along with Egger's and Begg's tests (p-values for maternal outcomes: 0.06 and 0.07 and neonatal outcomes: (0.83 and 0.28) did not indicate significant evidence for publication bias

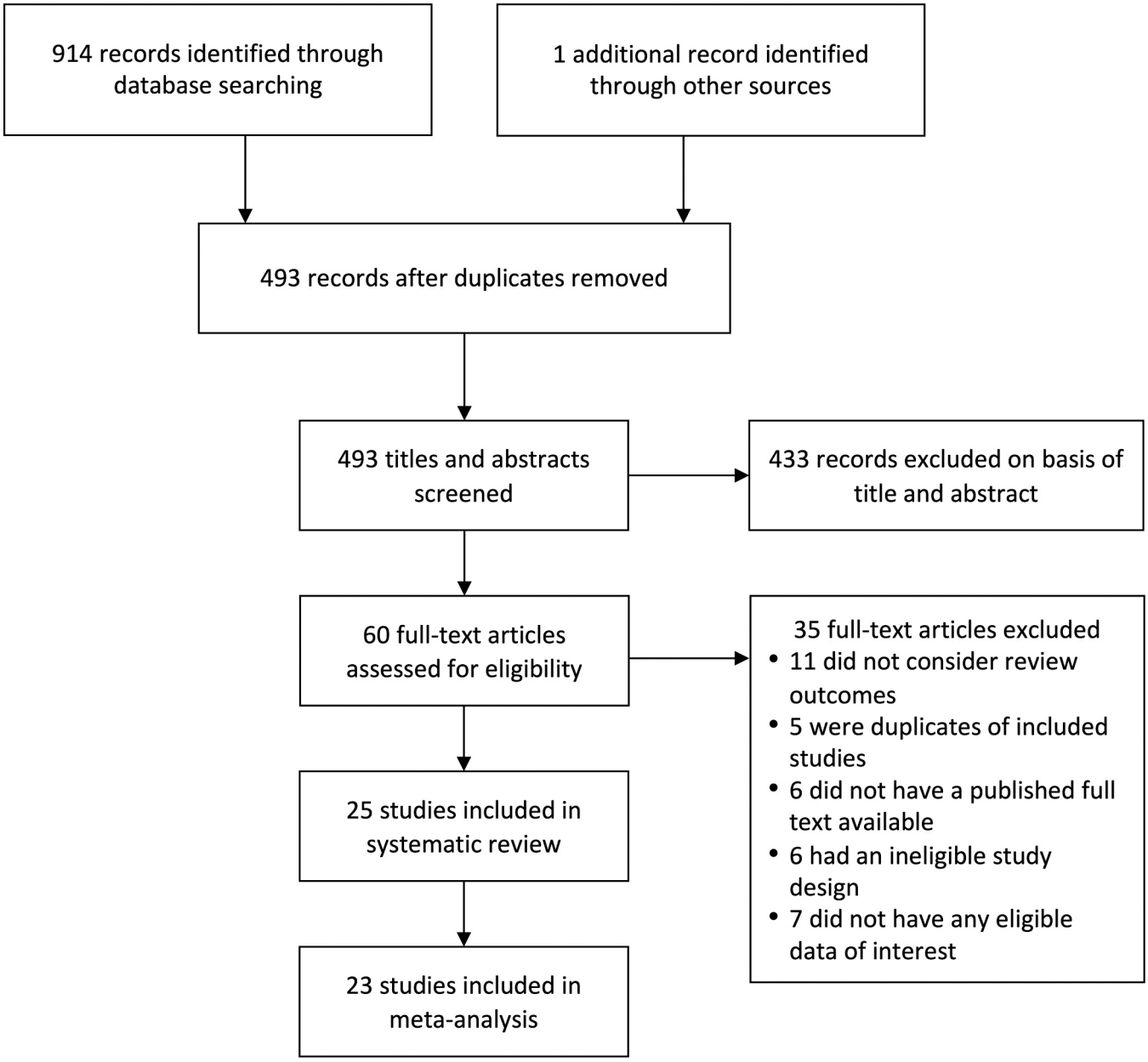

Fig. 1. Study selection process to identify studies considering the associations between vaping during pregnancy and perinatal outcomes.

(eFigure 1). Sensitivity analyses removing studies with a high risk of bias preserved these associations and reduced heterogeneity for both adverse maternal (I^2 = 63 %) and neonatal outcomes (I^2 = 53 %) (eFigure 2). Analyses removing multiple studies from similar cohorts also preserved associations and reduced heterogeneity for neonatal outcomes (I^2 = 33 %) (eFigure 3). Additionally, subgroup analyses considering confounding factors identified non-significant decreases in the strength of association for adjusted compared to unadjusted models for both maternal and neonatal outcomes (χ^2 test p-values: 0.45 and 0.67) (eFigure 4). There was a significant association for maternal but not neonatal outcomes for the less reported continuous outcomes (eFigure 5).

Considering frequently reported individual maternal outcomes, vaping during pregnancy had associations with decreased breastfeeding (OR: 0.53; 95 % CI: 0.38–0.72; I^2 = 45 %) and decreased prevalence of adequate prenatal care (OR: 0.69; 95 % CI: 0.56–0.86; I^2 = 82 %), but not for depression, gestational diabetes, or gestational hypertension (Fig. 3). In contrast, prenatal vaping was associated with frequently reported adverse neonatal outcomes, such as LBW (OR: 1.56; 95 % CI: 1.28–1.90; I^2 = 15 %), preterm birth (OR: 1.49; 95 % CI: 1.27–1.76; I^2 = 0 %), and SGA (OR: 1.48; 95 % CI: 1.16–1.89; I^2 = 70 %) (Fig. 4). A summary table for all meta-analyses (eTable 10) and additional forest plots for individual maternal (eFigure 6) and neonatal outcomes (eFigure 7) are included in the appendix.

Studies included in the narrative synthesis [43,47] generally demonstrated comparable findings to those included in the meta-analysis for both maternal and neonatal outcomes, except for one study [43], which differed due to a small sample of vaping users (n = 12) without any reported cases of SGA, making it ineligible for meta-analysis (since an OR could not be calculated).

3.4. Quality assessment

Individual studies mostly had a low risk of bias (11 studies), with five studies having some concerns about bias and seven studies having a high risk of bias (eFigure 8). Risk of bias was most frequently due to concerns

Table 1
Characteristics of included studies considering the associations between vaping during pregnancy and perinatal outcomes.

Study	Study design (follow-up)	Country	Maternal age (years)	Nonusers (n)	Vaping (n)	Cohort
Cardenas et al., [25] 2019	Prospective cohort (duration of pregnancy)	United States	18 to ≥ 28	64	6	Mothers attending a low-risk, university-affiliated pregnancy clinic in Little Rock, Arkansas
Cardenas et al., [43] 2020[a]	Retrospective cohort[b]	United States	≤ 19 to ≥ 35	1062	18	2016–2017 Arkansas PRAMS
Froggatt et al., [38] 2020	Retrospective case-control	United Kingdom	Vaping: 22.60 ± 5.52 Controls: 28.84 ± 4.86	44	10	White, full-term infants in a study with a university hospital in Middlesbrough, England
Kim and Oancea [26], 2020	Retrospective cohort[b]	United States	Vaping: 27 (22−32) Controls: 27 (27−32)	51,430	337	PRAMS Phase 8 (2016–2017) data of 36 states, New York City, and Puerto Rico
McDonnell et al., [20] 2020	Prospective cohort (duration of pregnancy)	Ireland	Vaping: 31 ± 5.3 Controls: 33 ± 5.9	108	218	Mothers attending a large maternity hospital in Dublin, Ireland
Rollins et al., [52] 2020	Cross-sectional	United States	Vaping: 26.8 ± 5.6 Controls: 27.0 ± 5.2	939	54	Pregnant women attending a low-income, urban clinic in Providence, Rhode Island
Wang et al., [27] 2020	Retrospective cohort[b]	United States	< 20 to ≥ 35	28,770	126	2016 PRAMS
Ashford et al., [39] 2021	Prospective cohort (duration of pregnancy)	United States	18–44	6	8	Pregnant former smokers attending academic and private prenatal clinics in Lexington, Kentucky
McBride and Haile [48], 2021	Retrospective cohort[b]	United States	< 20 to > 34	42,405	421	PRAMS Phase 8 (2016–2018)
Opondo et al., [19] 2021	Cross-sectional	United Kingdom	30.8 ± 5.6	4322	99	2018 NMS
Regan and Pereira [28], 2021	Retrospective cohort[b]	United States	18 to ≥ 40	8938	189	PRAMS Phase 8 (2016–2018) of 38 PRAMS sites for women who smoked in the two years before pregnancy
Regan et al., [29] 2021	Retrospective cohort[b]	United States	18 to ≥ 40	76,113	329	PRAMS Phase 8 (2016–2018) of 37 states and New York City
Galbo et al., [30] 2022	Retrospective cohort[b]	United States	< 19 to ≥ 35	71,081	859	PRAMS Phase 8 (2016–2017) of 47 states, the District of Columbia, and Puerto Rico
Hawkins et al., [31] 2022	Retrospective cohort[b]	United States	< 20 to ≥ 35	51,153	301	PRAMS Phase 8 (2016–2017) of 32 states
Lavezzi et al., [47] 2022[a]	Retrospective case-control	Italy	< 20 and ≥ 20	29	5	Stillborn babies collected under Italian law investigating SIUDS
Shittu et al., [32] 2022	Retrospective cohort[b]	United States	≤ 19 to ≥ 30	86,392	1184	PRAMS Phase 8 (2016–2018)
Wang et al., [33] 2022	Retrospective cohort[b]	United States	< 20 to ≥ 35	89,908	406	PRAMS Phase 8 (2016–2018)
Ammar et al., [34] 2023	Retrospective cohort[b]	United States	≤ 24 to ≥ 35	173,574	977	PRAMS Phase 8 (2016–2020) of 45 states, the District of Columbia, New York City, and Puerto Rico
Cohn et al., [17] 2023	Retrospective cohort[c]	United States	18 to ≥ 35	732	69	PATH Study Waves 1–5 (2013–2019)
Lin et al., [49] 2023	Retrospective cohort[c]	United States	18–44	728	41	PATH Study Waves 1–4 (2013–2018)
Nanninga et al., [35] 2023	Cross-sectional	The Netherlands	17–44	1706	10	Online survey of Dutch women who were pregnant between February 2019 and May 2022
Wang et al., [36] 2023	Retrospective cohort[b]	United States	< 20 to ≥ 35	1856	109	PRAMS Phase 8 (2016–2018) of Arkansas, Georgia, Iowa, Utah, Virginia, Vermont, and West Virginia for women who smoked in the three months before pregnancy
Wen et al., [18] 2023a	Retrospective cohort[b]	United States	10–19	9432	152	PRAMS Phase 8 (2016–2021) subgroup analysis of adolescents
Wen et al., [50] 2023b	Retrospective cohort[b]	United States	≤ 19 to ≥ 30	160,956	921	PRAMS Phase 8 (2016–2020)
Choi et al., [51] 2024	Retrospective cohort[b]	United States	< 20 to > 34	55,076	703	PRAMS Phase 8 (2016–2019)

Maternal age is presented as ranges, means ± standard deviations, or medians (interquartile ranges) as described by included studies. PRAMS indicates Pregnancy Risk Assessment Monitoring System; NMS, National Maternity Survey; SIUDS, Sudden Intrauterine Unexplained Death Syndrome; PATH, Population Assessment of Tobacco and Health.

[a] Study included in systematic review but not meta-analyses;
[b] Mothers initially contacted for surveys 2–4 months following birth;
[c] Mothers contacted for follow-up in the subsequent study wave.

with confounding and exposure assessment (20 and 21 studies respectively having at least some concerns for these domains), generally for not sufficiently considering reproductive history as a confounding factor, having limited quantitative measurement of vaping exposure, and not adequately accounting for smoking history in participants. The GRADE assessments raised minimal concerns about the certainty of the evidence for the main outcomes considered (eTable 11).

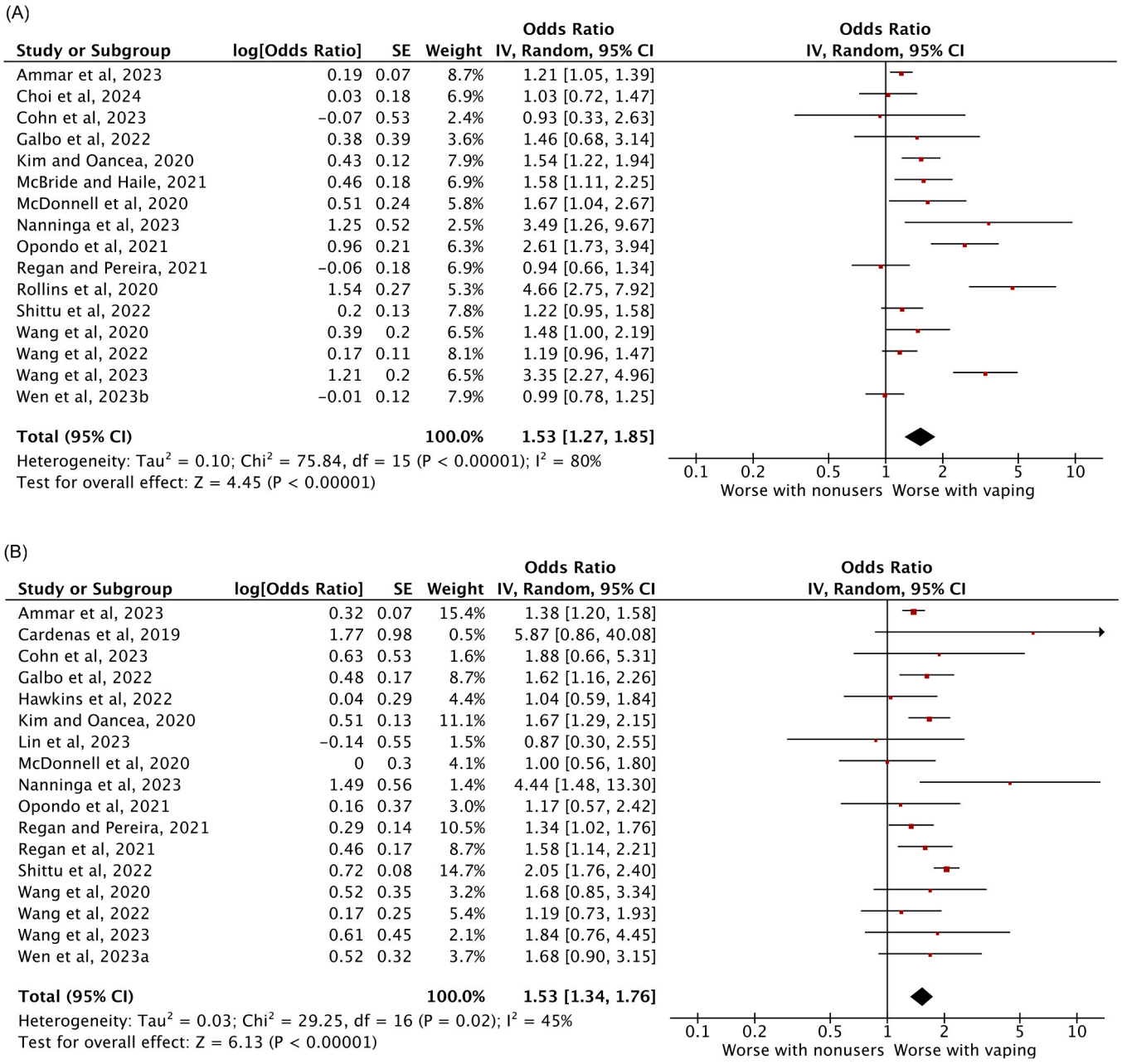

Fig. 2. Associations between vaping during pregnancy and the odds of adverse maternal and neonatal outcomes. (A) Maternal outcomes. (B) Neonatal outcomes. OR indicates odds ratio; CI, confidence interval; SE, standard error; IV, inverse variance.

4. Discussion

4.1. Principal findings and possible explanations

The findings of this systematic review and meta-analysis of 25 studies demonstrated that vaping during pregnancy was associated with 53 % increased odds of adverse maternal outcomes in a meta-analysis of 16 studies. In particular, prenatal vaping was significantly associated with 47 % lower odds of breastfeeding and 31 % lower odds of prenatal care; however, its associations with other maternal outcomes, such as depression, diabetes, and hypertension, were not statistically significant. Prenatal exposure to vaping was also associated with a similarly 53 % increased odds of adverse neonatal outcomes in a meta-analysis of 17 studies, specifically, with 56 % higher odds for LBW, 49 % higher odds of preterm birth, and 48 % higher odds of SGA. The quality assessments demonstrated that these results were generally robust to sensitivity analyses, concerns for bias in individual studies were generally around confounding factors and exposure assessment, and minimal concerns were raised regarding the certainty of synthesized evidence.

Among all maternal outcomes, prenatal care was the most frequently reported outcome influenced by prenatal vaping exposure. Although there is limited information on why pregnant women who vaped during pregnancy reported less access to prenatal care, one possibility is that prenatal vaping was not examined until the third trimester, which may have led to the omission of earlier prenatal care information in those reports. It is also important to note that, apart from prenatal care, there were significantly fewer studies addressing breastfeeding, depression, diabetes, and hypertension. As a result, the studies reporting these outcomes may have inherent biases, as indicated by the observed heterogeneity, and should therefore be interpreted with caution. Importantly, the prevalence of LBW, preterm birth, and SGA were intimately related to prenatal exposure to vaping. Our findings indicate that

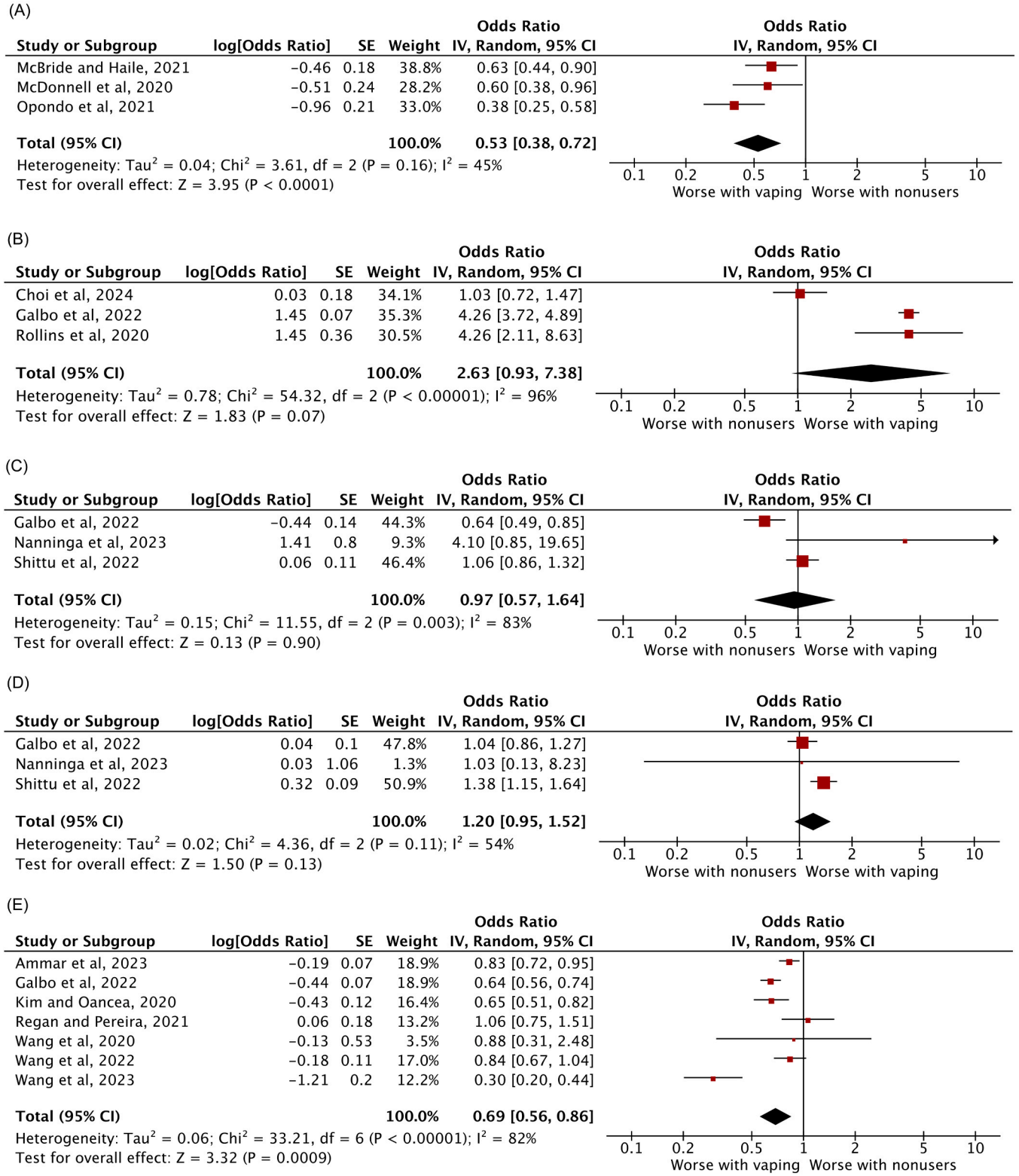

Fig. 3. Associations between vaping during pregnancy and the odds of individual adverse maternal outcomes. (A) Breastfeeding. (B) Depression. (C) Diabetes. (D) Hypertension. (E) Prenatal care. OR indicates odds ratio; CI, confidence interval; SE, standard error; IV, inverse variance.

prenatal vaping has a stronger influence on neonatal outcomes than on maternal outcomes. Although a recent systematic review (which was not a meta-analysis) examined the health outcomes associated with vaping during pregnancy [53], it only compared vaping to smoking and did not provide conclusive evidence of adverse pregnancy or neonatal outcomes related to vaping. Furthermore, there are very few studies that have systematically synthesized evidence on prenatal vaping and its effects on pregnancy-related outcomes, making it difficult to compare our findings with previous or contemporary research.

Although the pathophysiology of how vaping affects perinatal outcomes is not clear, possible explanations could be drawn from the health effects of constituent chemicals found in e-cigarettes. Chemical analyses

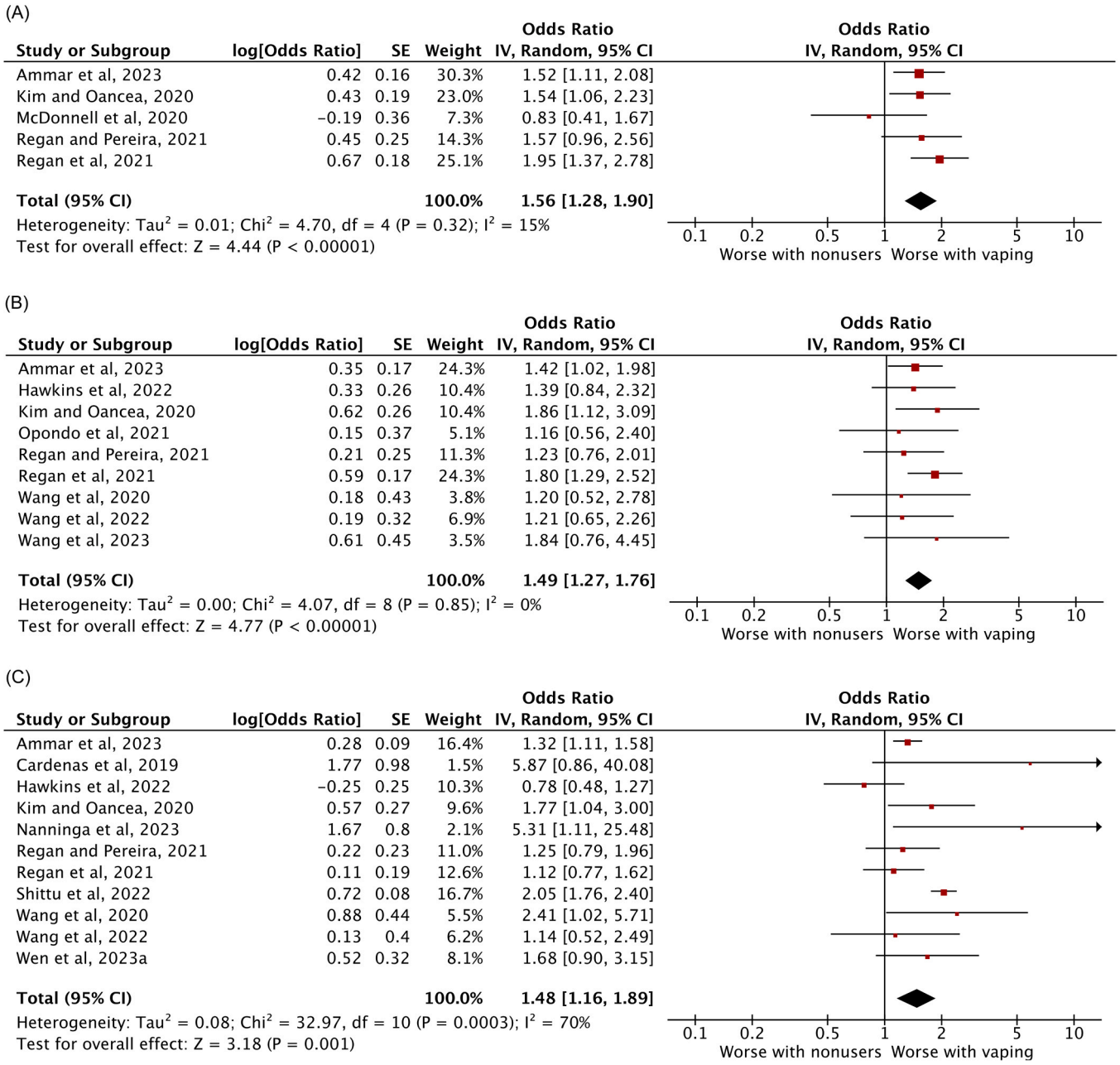

Fig. 4. Associations between vaping during pregnancy and the odds of individual adverse neonatal outcomes. (A) Low birthweight. (B) Preterm birth. (C) Small for gestational age. OR indicates odds ratio; CI, confidence interval; SE, standard error; IV, inverse variance.

of e-cigarette solutions have identified over 150 different chemicals, though the health effects of many of these are not established. Some of the most common e-cigarette materials are VOCs (e.g., benzene) and heavy metals [54–57], which have known and significant adverse health effects in humans. Two studies have shown that exposure to heavy metals in early pregnancy was associated with an increased risk of gestational hypertension [58,59]. Although little is known about whether benzene affects maternal outcomes, intrauterine benzene exposure is associated with a higher risk of preterm birth [60]. Similarly, heavy metal exposure during pregnancy has been shown to affect newborn health. Two birth cohort studies from Japan and Myanmar demonstrated that maternal body burden of heavy metals, particularly cadmium, was associated with a higher risk of LBW in newborns [61, 62]. Similar associations were observed between prenatal heavy metal exposure and both preterm birth [62–64] and SGA [65]. These findings are consistent with the respective 56 %, 49 %, and 48 % higher odds of LBW, preterm birth, and SGA we demonstrated with prenatal vaping. Although such evidence does not confirm that the use of e-cigarettes would have similar effects, it may serve as a foundation for future research on the mechanism of toxicity. However, the continuous release of new vaping devices and products makes it difficult to characterize the formulation and profile the cytotoxicity of associated solvents. While retrospective epidemiological studies primarily drove our analyses, more well-designed prospective studies are required to corroborate our findings. Additionally, while epidemiological studies provide preliminary evidence of the detrimental effects of vaping during pregnancy, more experimental research is necessary to gain the much-required mechanistic evidence behind the harms of vaping.

Although human studies related to vaping have not been able to provide much information about the potential mechanisms, animal studies have indicated that vaping during pregnancy can alter cerebrovascular function [66], and affect blood-brain-barrier integrity, and

negatively impact motor, learning, and memory function in the offspring [67], possibly by hampering the hippocampal mTOR (Mammalian Target of Rapamycin) signaling pathway [68]. Another study has shown that the use of e-cigarettes during pregnancy can also lead to long-term arterial stiffness in offspring [69], which may also play a significant role in long-term disabilities among offspring. E-cigarette liquids contain a cocktail of potentially hazardous chemicals known for their toxicological and immunological roles such as oxidative DNA damage, neutrophil activation, and apoptosis [70–74]. It must also be noted that the chemical compositions vary across devices and brands and many of those chemicals are yet to be tested for their potential toxicological effects. Therefore, more laboratory research is needed to identify these chemicals, study their physical and chemical characteristics, and assess their potential toxicological effects.

As evidence continues to suggest the potential harms of vaping, it is important to consider how these findings translate to the population level. As perinatal guidelines continue to appreciate the interactions between health behaviors for maternal and fetal health [24], research studies are needed to understand vaping as a health behavior for pregnant populations to best inform guidelines and help mothers navigate vaping and vaping exposure during pregnancy. For instance, since vaping and smoking are believed to have similar adverse effects on cardiorespiratory and muscle function in non-pregnant individuals (reducing exercise capacity) [75], vaping might also diminish the benefits of exercise on maternal and fetal health. Additionally, primary care providers should consider how to address vaping with patients during the perinatal period [76]. Also, it needs to be remembered that the use of e-cigarettes could be different across countries and may also be dependent on other factors such as socioeconomic conditions or cultural aspects. For example, e-cigarette use is higher among people with a lower socioeconomic background in some countries like the UK [77], whereas this is more popular among people with a higher socioeconomic status in countries like the US [78]. Therefore, the generalizability of the findings could be limited to the developed countries and may not be coherent. Nevertheless, there are almost no data available on prenatal vaping from developing countries; therefore, the generalizability of the findings is still to be established. Further research could reveal differences in perinatal vaping behaviors across groups and the unknown long-term outcomes for children [16]. Findings could inform public health campaigns, such as those in Australia [79], on regulating product sales, advertising health effects, and educating prenatal care providers.

4.2. Strengths and limitations

The major strength of our study is that it is the only complete meta-analysis assessing the associations between prenatal vaping and adverse perinatal outcomes. Unlike the only other meta-analysis on this topic (which exclusively considered SGA in a limited number of studies and was not peer-reviewed) [80], the present analyses differentially assessed both maternal and neonatal outcomes using pooled estimates, allowing for comparisons to be made across a broader range of studies, while individual analyses allowed for direct comparisons of specific outcomes assessed by multiple studies [81]. While systematic reviews have discussed the consequences of vaping during pregnancy [53,82–84], this study fills a major gap in the quantitative assessment of the effects of vaping exposure during pregnancy on prevalent health conditions experienced by women and neonates, offering cross-database comparisons and systematic assessments of how broader confounding factors could be contributing to such issues.

This analysis has some limitations. First, all reviewed literature is observational, which limits the ability to make causal conclusions and results in lower evidence certainty compared to experimental designs, a known limitation when experimental studies are ethically or practically unfeasible [31,44]. For exposure assessment, all but two studies [33,49] categorized and analyzed vaping exposure into either user or nonuser groups and did not have a quantitative evaluation of exposures. Nevertheless, different from cigarette smoking, it is difficult to quantify vaping as the size, quantity of liquid, and contents of vaping solutions can widely vary. Additionally, many studies relied on self-reported data at single time points, making it unclear whether vaping was continuous during pregnancy or varied across trimesters. The retrospective design of a large proportion of included studies [17,18,26–34,36,38,43,47–51] introduces potential recall bias, especially if women vaped before pregnancy was confirmed, potentially affecting the inclusion of adverse effects. In such cases, any adverse effects may or may not have been incorporated into those studies. Also, most studies recorded vaping during pregnancy as a dichotomous exposure (yes/no) rather than a continuous exposure (an actual measurement of the quantity of vaping). Therefore, a meta-regression of dose-dependent effects was not possible to estimate in this analysis. Although we performed sensitivity analyses to consider the influence of the confounders by taking the adjusted estimates, the confounders significantly varied across studies. Therefore, we could not focus much on the adjusted analysis. Nevertheless, our results do not indicate a substantial change in the estimates between unadjusted and adjusted effects, indicating vaping during pregnancy as a risk factor for adverse perinatal outcomes. While a significant number of studies were from the United States and analyzed different outcomes, sensitivity analyses excluding these studies still showed consistent results. The lack of comprehensive surveys on vaping in many countries may hinder the identification of vaping as a risk factor globally. Finally, our search strategy did not systematically include grey literature or non-indexed journals, which might mean some relevant studies were missing.

5. Conclusions

This systematic review and meta-analysis provides strong evidence that prenatal vaping may increase the odds of adverse maternal and neonatal outcomes, including LBW, PTB, and SGA. The risks are likely to arise from toxic substances, such as VOCs and heavy metals, found in e-cigarette solutions. Although the underlying mechanisms remain unclear, experimental and epidemiological studies suggest the involvement of oxidative stress, vascular dysfunction, and developmental impacts on offspring. This analysis emphasizes the need for prospective studies and mechanistic research to confirm these associations. Public health initiatives should aim at raising awareness of the risks associated with prenatal vaping and promoting healthier maternal health behaviors to minimize exposure and improve perinatal outcomes.

Environmental implications

Vape or electronic cigarettes (e-cigarettes) contain hazardous heavy metals such as lead, cadmium, and nickel, which are potential carcinogens. These toxic chemicals not only pose credible threats to mothers and their unborn babies, but their disposal also significantly impacts the environment by contaminating the soil and water. Moreover, e-cigarettes also contain flavoring agents such as diacetyl, a known causal agent for interstitial lung diseases (ILDs). Although the bystander effects of vaping are not yet known, it can be perceived that these harmful chemicals emanating from vaping devices impart significant passive effects on non-users, children, elderly, and people with respiratory conditions.

Ethical approval

Not required.

Funding/Support

Andy Deprato received a summer studentship from the Northern Alberta Clinical Trials and Research Centre during the study and a travel award from the Canadian Institute of Health Research Institute of

Circulatory and Respiratory Health (CIHR-ICRH) and the Canadian Lung Association. The study is partially supported by an unrestricted research grant from Synergy Respiratory and Cardiac Care to Paige Lacy. The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Data sharing statement

The data used in the analyses included in this article are publicly available. Data can be accessed directly from the literature referenced in this article. Extracted data from included studies used in analyses can be made available to researchers who provide a methodologically sound and reasonable proposal. Proposals should be directed to the corresponding author.

Conference presentation

A subset of related study data was presented at the 16th Annual Canadian Respiratory Conference in Toronto, Ontario, Canada on April 12, 2024.

CRediT authorship contribution statement

Subhabrata Moitra: Writing – review & editing, Visualization, Validation, Supervision, Software, Project administration, Methodology, Investigation, Data curation, Conceptualization. **Paige Lacy:** Writing – review & editing. **Margie H. Davenport:** Writing – review & editing. **Padma Kaul:** Writing – review & editing. **Danila Azzolina:** Writing – review & editing. **Nicola Murgia:** Writing – review & editing. **Andy Deprato:** Writing – original draft, Validation, Software, Methodology, Investigation, Formal analysis. **Arundhati Garud:** Writing – review & editing, Software.

Declaration of Competing Interest

Nicola Murgia reports non-financial support from GSK, AstraZeneca, Chiesi Farmaceutici, and Menarini outside the submitted work. Margie H Davenport reports grants from the Natural Sciences and Engineering Research Council of Canada (NSERC), Social Sciences and Humanities Research Council (SSHRC), International Olympic Committee (IOC), and Women and Children's Health Research Institute outside the submitted work. She is the Christenson Professor in Active Healthy Living. Padma Kaul holds a Canadian Institute of Health Research (CIHR) Sex and Gender Science Chair and a Heart & Stroke Chair in Cardiovascular Research. Paige Lacy reports grants from the Wellness of Workers (WoW) Program, Local 110 Heat & Frost Insulators & Allied Workers, Synergy Respiratory and Cardiac Care, AstraZeneca Canada, and the Natural Sciences and Engineering Research Council of Canada (NSERC) during the conduct of the study and personal fees from AstraZeneca Canada and GSK Canada outside the submitted work. Subhabrata Moitra reports personal fees from Elsevier (USA), Synergy Respiratory and Cardiac Care (Canada) and Permanyer Inc. (Spain), and lecture fees from Apollo Multispeciality Hospitals (India) and the Institute of Allergy – Kolkata (India) outside the submitted work. All other authors do not have any disclosures to report.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jhazmat.2024.137028.

Data availability

Data will be made available on request.

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