Fetal Exposure to Nicotine-Containing E-Cigarettes and the Risk of Childhood Asthma

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Electronic cigarettes (e-cigarettes) use has increased drastically in recent years, becoming the most used tobacco product among youth and the second most used among adults in the United States (U.S. Department of Health and Human Services [HHS], 2024). Marketed as a safer alternative to traditional cigarettes or as nicotine replacement therapies (NRTs), e-cigarettes still contain nicotine, a highly addictive substance that is toxic to developing fetuses (Centers for Disease Control and Prevention [CDC], 2025). Despite these perceptions of reduced harm, e-cigarette aerosols contain other harmful substances, including volatile organic compounds, reactive oxygen species, and heavy metals that contribute to oxidative stress and inflammation in the lungs (CDC, 2024; Rebuli et al., 2023).

Animal studies show that prenatal nicotine exposure with e-cigarette use disrupts fetal lung development and activates inflammatory pathways linked to asthma susceptibility (Tsai et al., 2021; Wang et al., 2020). Similarly, human data suggest that e-cigarette use during pregnancy increases the risk of low birth weight and preterm birth, even among non-smoking mothers exposed to secondhand e-cigarette aerosols (Regan et al., 2021). These findings highlight the potential for lasting respiratory effects in children exposed to nicotine in utero.

Asthma remains one of the most prevalent chronic diseases of childhood (HHS, 2024), and identifying modifiable prenatal risk factors is essential for prevention. As e-cigarette use among pregnant individuals increases, understanding the long-term effects of fetal exposure is critical to guide public health recommendations and inform clinical counseling. This literature review explores how fetal exposure to nicotine-containing e-cigarettes, compared to no exposure, influences the risk of asthma development in children. Investigating this issue addresses a critical and timely gap in clinical understanding.

Search Strategy

The literature search was systematic, efficient, and thorough, utilizing keywords derived from the PICOT question, inclusion/exclusion criteria, synonyms, subject headings, expanded search options, Boolean connectors, and relevant limits (Melnyk & Fineout-Overholt, 2022). The PICOT keywords included: 'In children (P), how does fetal exposure to nicotine-containing e-cigarettes (O), compared to no exposure (C), influence asthma risk (O)?' Additional related terms included 'children (P),' 'fetal exposure to e-cigarettes,' and 'asthma,' as shown in Appendix A, Table A1. Search strategies employed various databases, including Google Scholar, CINAHL, PubMed, Strauss Library, using keywords and synonyms (see Appendix A, Table A2 and Table A3) linked by Boolean operators (OR/AND). Searches were limited to the past five years to ensure relevance and novelty.

Each author independently reviewed abstracts, discussions, and conclusions of the evidence to compile initial literature lists (total studies = 32). These reviews were subsequently cross verified by two additional authors. The combined literature was then filtered using inclusion criteria: studies involving pregnant persons and fetal e-cigarette exposure and asthma, and exclusion criteria: second- and third-hand smoke exposure and/or adolescent smoking. The final selection involved group discussions among the three authors, resulting in 8 studies after removing duplicates. Efforts were made to include various evidence levels, including at least one systematic review or meta-analysis, multiple random control trials (RCTs), qualitative or metasynthesis studies on patient perceptions, clinical practice guidelines or consensus papers, and relevant nonexperimental studies (cohort, case-control). Due to the emerging nature of e-cigarette research, longitudinal studies were not identified. Narrative reviews were also not included due to the nature of this research paper. Additionally, no RTCs were located or identified due to ethical reasons.

All selected studies were reviewed in full and analyzed by the authors with evidence and synthesis tables. Notably, the PICOT question was revised to include 'nicotine' because most evidence was linked with nicotine smoking mechanisms and not the specific type of smoking. Additionally,

insufficient evidence was available specifically on e-cigarette harm and asthma outcomes, prompting the inclusion of additional sources relevant to nicotine exposure.

Literature Review

Krist et al. (2021) completed a clinical review for the US Preventive Services Task Force (USPSTF), analyzing data from hundreds of systematic reviews and randomized controlled trials (n > 500,000) on smoking cessation interventions. The clinical review indirectly supports our PICOT question, as it shows e-cigarette safety/efficacy in pregnancy is uncertain and reinforces the need to avoid fetal nicotine exposure. Behavioral counseling and US Food and Drug Administration (FDA)-approved pharmacotherapies, including NRTs, bupropion, and varenicline, demonstrated substantial benefits in nonpregnant adults, especially when combined. For pregnant persons, behavioral counseling improved cessation rates, but the evidence on pharmacotherapy and e-cigarettes was limited and inconclusive. The analysis found that physician and nurse advice, group or phone counseling, and mobile-based interventions increased quit rates with minimal harm. Overall, the clinical review shows strong level 1 evidence, transparent synthesis, and clinically actionable recommendations. However, its limitations include low-quality data on e-cigarettes in pregnancy, with a focus only on cessation (Krist et al., 2021).

Agache et al. (2024) conducted a systematic review and meta-analysis under Preferred Reporting Items for Systemic Review Meta-Analysis (PRISMA) guidelines to assess the effects of tobacco smoke and e-cigarette exposure on asthma-related outcomes. Drawing on 113 studies with more than 800,000 global participants, the authors compared prenatal, postnatal, and active exposures with no exposure. Prenatal environmental tobacco smoke (ETS) significantly increased the risk of new-onset asthma (OR 1.28; 95% CI 1.18–1.39) and recurrent wheezing (OR 1.43; 95% CI 1.30–1.56). Using the GRADE approach, the study confirmed high certainty that both combustible and electronic nicotine exposures contribute to pediatric asthma and poor asthma control (Agache et al., 2024). This study demonstrated methodological rigor and consistent findings across exposure types and supports a causal

link between nicotine exposure and adverse respiratory outcomes. However, the strength of the study is limited by subgroup analyses and residual heterogeneity. Despite these weaknesses, the large sample size and the transparency in the GRADE assessment made this a high-quality source of evidence.

Deprato et al. (2025) performed a PRISMA guided systematic review and meta-analysis on prenatal vaping and adverse perinatal outcomes. Combining 23 studies with 924,376 participants, the authors found that vaping during pregnancy increased the odds of both maternal and neonatal adverse outcomes by 53% (OR 1.53; 95% CI 1.27–1.85 for maternal; OR 1.53; 95% CI 1.34–1.76 for neonatal). Specific risks included low birth weight (OR 1.56), preterm birth (OR 1.49), and small for gestational age (OR 1.48). While heterogeneity and self-reported vaping behaviors introduce potential bias, sensitivity analyses supported the stability of the findings. Most included studies were observational and subject to residual confounding, which limits causal inference (Deprato et al., 2025). Even so, this review provides the strongest available human evidence that prenatal e-cigarette exposure is linked to clinically meaningful perinatal morbidity, outcomes that are known to elevate later respiratory and asthma risk despite asthma not being evaluated directly.

Wang et al. (2024) used a Mendelian randomization design with genome-wide association data from 494,132 participants to evaluate the causal effects of maternal smoking on offspring respiratory diseases. After removing twelve confounding single nucleotide polymorphisms, findings revealed a significant association between maternal smoking and offspring asthma (OR 1.336; 95% CI 1.161–1.538; $p < 0.001$), supporting a genetic causal link between prenatal tobacco exposure and respiratory dysfunction. The study also connected in-utero nicotine exposure with chronic airway inflammation and adult respiratory disease. Limitations included the predominance of European ancestry data and potential bias from unaccounted developmental or environmental factors. Additionally, the study identifies risk related to nicotine exposure and does not differentiate between nicotine from e-cigarettes or nicotine from combustible cigarettes, limiting the applicability of this study. Using large

GWAS datasets and causal frameworks, results provide strong genetic evidence that fetal nicotine exposure disrupts lung development and elevates lifelong respiratory risk (Wang et al., 2024).

Sunde et al. (2021) conducted a longitudinal cohort study within the COPSAC2000 cohort to examine prenatal tobacco exposure and child asthma and allergy outcomes. The study directly supports our PICOT question as it shows prenatal tobacco exposure alone (nicotine + smoke) is sufficient to increase asthma, exacerbation, and lung function impairment in childhood via structural, not allergic, mechanisms. Among 411 children born to mothers with asthma, exposure was validated through cotinine levels in newborns and hair nicotine at one year. Prenatal tobacco exposure doubled the risk of asthma (aHR 2.05; 95% CI 1.13–3.73) and LRTIs (aIRR 1.87) and tripled exacerbation risk (aHR 3.76). It was also linked to reduced lung function (aMD –0.07 L) and increased bronchial responsiveness, though no associations were found for allergy or atopic dermatitis. The genotype 17q12–21 modulated the asthma effect, suggesting developmental rather than allergic mechanisms. Limitations of the study included modest sample size; high-risk (maternal asthma) cohort; some self-reported exposure; and limited generalizability. Despite reliance on self-reporting, objective biomarkers enhanced study validity and reliability (Sunde et al., 2021).

Galbo et al. (2022) conducted a retrospective cohort study of women who smoked e-cigarettes during pregnancy and those who did not (n=71,940). The study was based on responses from participants in the 2016 and 2017 Pregnancy Risk Assessment Monitoring System (PRAMS) and Phase 8 core surveys. The study indirectly supports our PICOT question as it revealed an association between e-cigarette use in pregnancy and unfavorable birth outcomes. However, it does not address asthma or the fetus's later-life respiratory outcomes. The participant sample was assessed for baseline characteristics, nominal variables summarized as percentages, and continuous variables analyzed using mean and standard deviations, and median and interquartile ranges for normal distributions and non-normal distributions, respectively. Researchers discovered a 62% higher rate in the odds of unfavorable birth

outcomes for women who smoked e-cigarettes compared to those who did not (aOR 1.62, 95% CI: 1.16-2.26, p-value = 0.005). Although this study used a strong standardized PRAM data collection, limitations included recall and non-response bias and self-reporting. Additionally, data did not cover the entirety of pregnancy, only the last 3 months for smoking duration and length of stay. Underrepresented data may also be a factor due to the grouped rating of 3-5 days in hospital, with only a 5-day hospital stay equating to an unfavorable birth outcome. Overall, this study's findings highlight the need for continued research on the effects of e-cigarette smoking on the fetus, with particular importance on adverse respiratory outcomes (Galbo et al., 2022).

Froggatt et al. (2021) conducted an exploratory qualitative study in North East England with 14 postpartum women who smoked during pregnancy. The study indirectly supports our PICOT question as it shows behavioral support but does not answer asthma outcome directly; it shows pregnant smokers often misunderstand e-cigarette risks, which influences fetal exposure patterns. Interviews revealed two primary themes for cigarette use: justification and health, and six for e-cigarettes: uncertainty, personal experience, comparison, product characteristics, received advice, and perceived healthiness. Most participants believed e-cigarettes were potentially more harmful during pregnancy due to unknown risks, leading to the rationalization of continued smoking over cessation. Although limited by a small sample size and potential bias, the study illuminated perceptions that hinder cessation and reflect confusion surrounding e-cigarette safety in pregnancy (Froggatt et al., 2021). These findings emphasize the need for clearer health messaging to correct misconceptions about e-cigarettes as safer alternatives.

Ozekin et al. (2023) conducted an in vivo animal experiment to investigate the effects of maternal exposure to nicotine-containing e-cigarette vapor on fetal respiratory development. Pregnant mice were exposed to 2.4% nicotine vapor for four hours daily throughout gestation. Exposed fetuses exhibited growth restriction, reduced airspace, impaired ciliated cell differentiation, and disrupted developmental signaling pathways (Wnt, BMP/TGF-β, Notch, Hedgehog). Additional defects in bone and

craniofacial growth were observed, particularly in genetically susceptible (Kcnj2KO/+) strains. Although not assessing postnatal respiratory function, the study provides mechanistic evidence that prenatal nicotine vapor exposure disrupts fetal lung formation and may predispose offspring to respiratory disease. Nonetheless, the study provides biologically plausible evidence that fetal exposure to nicotine-containing e-cigarette aerosols may predispose offspring to later respiratory vulnerability (Ozekin et al., 2023).

Evidence Synthesis

Across molecular, animal, and human studies, the evidence collectively shows that prenatal nicotine exposure disrupts fetal lung development and elevates the risk of respiratory disease in childhood, including asthma. Mechanistic research provides clear biological pathways for this risk. Ozekin et al. (2023) demonstrated that nicotine-containing e-cigarette vapor impairs distal lung branching and alters expression of developmental genes in fetal mice, findings that reflect direct interference with airway maturation and cellular differentiation. These disruptions form a biologically plausible foundation for later respiratory vulnerability.

Human studies closely mirror these mechanistic patterns. Sunde et al. (2021) reported that prenatal smoking exposure doubled the risk of asthma by age seven and increased early-life exacerbations and lower respiratory infections. Agache et al. (2024) synthesized global data and similarly found increased odds of new-onset asthma and recurrent wheezing among children exposed to prenatal environmental tobacco smoke. Molecular evidence from Wang et al. (2024) adds further support by demonstrating a more than thirty percent increase in asthma risk associated with prenatal nicotine exposure in genetically susceptible offspring.

Although fewer human studies isolate vaping-only exposure, the available research indicates patterns consistent with nicotine-related harm. Galbo et al. (2022) analyzed more than seventy-one thousand pregnancies and found that e-cigarette use during the final trimester was associated with a

sixty-two percent increase in the odds of unfavorable birth outcomes, including low birth weight and preterm birth, outcomes known to increase long-term respiratory risk. Despite limitations such as self-reported exposure and incomplete information about vaping throughout the full pregnancy, the study contributes important human evidence suggesting that prenatal e-cigarette use may compromise fetal health.

Taken together, these findings form a coherent pattern in which nicotine exposure in utero, regardless of delivery method, interferes with respiratory development and increases vulnerability to asthma. At the same time, meaningful gaps remain. Very few studies directly evaluate long-term respiratory outcomes following exclusive prenatal e-cigarette exposure. This lack of data is consistent with broader clinical reviews. Krist et al. (2021) concluded that evidence is insufficient to determine the safety or effectiveness of e-cigarettes for smoking cessation during pregnancy. Qualitative work by Froggatt et al. (2021) further reflects this uncertainty, as pregnant individuals reported perceiving e-cigarettes as risky due to limited knowledge about fetal impacts.

While the evidence for combustible tobacco exposure is extensive and consistently points to increased asthma risk, emerging molecular and epidemiologic findings suggest that nicotine-containing e-cigarettes may carry similar risks for fetal respiratory development. The collective research supports a clear concern about prenatal nicotine exposure and emphasizes the need for targeted investigation into the long-term respiratory consequences of maternal vaping.

Discussion

Each author independently reviewed the literature to determine whether prenatal exposure to nicotine-containing e-cigarettes, compared with no exposure, increases the risk of developing childhood asthma. Collectively, the evidence across studies supports our PICOT question, indicating a consistent association between fetal nicotine exposure and adverse respiratory outcomes. Although the overall certainty of evidence remains low due to the limited number of longitudinal human studies isolating e-

cigarette exposure (Agache et al., 2024), the direction of findings consistently points toward an increased risk. This is supported by mechanistic evidence demonstrating disrupted fetal lung development (Ozekin et al., 2023), perinatal associations linking prenatal vaping to compromised respiratory outcomes (Deprato et al., 2025), and epidemiological data connecting prenatal tobacco exposure to a higher incidence of childhood asthma (Sunde et al., 2022).

Beyond this overall trend, there is substantial human evidence across multiple study designs supporting the relationship between in-utero exposure to maternal vaping and an increased risk of childhood asthma. Although direct longitudinal human studies examining vaping in pregnancy and childhood asthma are lacking, consistent patterns emerge across molecular, animal, and population-based research. For example, observational cohort studies and systematic reviews demonstrate that maternal vaping and nicotine exposure elevate the odds of asthma and recurrent wheezing in offspring (Agache et al., 2024) and highlight nicotine's adverse effects on fetal lung and immune development (Sunde et al., 2022). In addition, Wang et al. (2024) provided causal genetic evidence that maternal nicotine exposure increases the risk of asthma and chronic respiratory disease in offspring. Galbo et al. (2022) research further strengthens the concern that fetal exposure to e-cigarette aerosols, which commonly contain nicotine, is associated with preterm birth and low birth rate. These outcomes reflect impaired fetal growth and provide human evidence supporting later respiratory harm. Collectively, these outcomes reinforce the biological plausibility that fetal nicotine exposure from maternal vaping disrupts physiological development that is essential for healthy respiratory maturation. In parallel, experimental and animal studies further reinforce the mechanistic plausibility of harm. Ozekin et al. (2023) demonstrated that maternal nicotine vaping disrupts embryonic lung and skeletal development, leading to airway hyperreactivity and asthma-like phenotypes in offspring. These findings strongly support a causal pathway between in-utero nicotine aerosol exposure and subsequent airway disease. Despite the overall consistency of evidence pointing toward harm, qualitative and guideline studies (Froggatt et al.,

2021; Krist et al., 2021) highlight ongoing uncertainty. Both emphasize limited public and clinical confidence due to insufficient data on e-cigarette use during pregnancy. Moreover, these investigations did not directly differentiate nicotine-containing from nicotine-free e-cigarettes, leaving the specific risk magnitude of nicotine-containing products inconclusive. Nonetheless, the direction of evidence continues to align with the PICOT question, indicating that fetal exposure to nicotine-containing e-cigarettes increases the risk of developing childhood asthma, even though the precise degree of risk remains uncertain.

Conclusion

There is currently no direct human evidence that isolates prenatal nicotine vaping and tracks offspring to a clinically confirmed asthma diagnosis. However, a consistent pattern emerges from related evidence: pregnant vapers experience perinatal complications, mechanistic studies demonstrate nicotine-aerosol injury to the developing lung, and extensive epidemiologic research on prenatal tobacco exposure confirms adverse respiratory outcomes. This convergence of findings leans toward harm and justifies a precautionary stance.

Given the insufficient human evidence to definitively answer our PICOT question, further prospective cohort studies with biomarker-verified nicotine exposure, clear differentiation between nicotine-free and nicotine-containing e-cigarettes, and standardized asthma outcome measures are urgently needed (Agache et al., 2024; Krist et al., 2021).

Overall, this body of evidence suggests that prenatal nicotine exposure contributes to asthma development and impaired lung function. For clinical practice, this underscores the importance of counseling against e-cigarette use in pregnancy, emphasizing behavioral cessation strategies, and reinforcing that vaping is not a safe alternative to smoking. Nurse practitioners can apply structured cessation approaches - such as the 5 A’s (Ask, Advise, Assess, Assist, Arrange), motivational interviewing, referral to quit lines, and offering evidence-based smoking cessation therapies - to actively engage

patients and provide ongoing support throughout the quitting process (Gilbert et al., 2025). These proactive, evidence-based counseling strategies are critical for reducing nicotine exposure in pregnancy and protecting long-term respiratory outcomes in children.

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Appendix A

Table A1:

PICO(T) Question Breakdown

Outcome	asthma
Intervention	fetal exposure to e-cigarettes CHANGED TO fetal exposure to nicotine-containg e-cigarettes
Comparison	not applicable for this literature review
Population	children
Time	not applicable for this literature review

Table A2:

PICO(T) Search Stratigies

PICO(T) Element	Keyword	Synonyms
Outcome	asthma	bronchial inflammation, asthma attack, asthmatic, lung, lung disease, chronic lung disease, asthma exacerbation(s)
Intervention	fetal exposure to e-cigarettes fetal exposure to nicotine-containing e-cigarettes pregnant	embryo development, subjection, fetus, prenatal exposure delayed effects, in-utero, in *vivo*, in *vitro* vaping, vapes, electronic nicotine delivery systems, e-cigs aerosol(s), e-cigs, electronic cigarette(s), nicotine maternal, pregnancy, pregnant woman, pregnant person, mothers, mother's perceptions,
Comparison	-	not applicable for this literature review
Population	children	kids, pediatrics, adolescents, school-aged, toddlers, infants, preschoolers, offspring
Time	-	not applicable for this literature review

Table A3:

Additional Search Stratigies

Additional Search Terms Used:	systematic review, randomized control trial, RCTs, practice guidelines, guidelines, analysis, clinical trials, qualitative, metasynthesis, case-control, cohort

Appendix B

University of Colorado College of Nursing

Anschutz Medical Campus

Evidence Table

Problem Statement: Limited evidence exists on how fetal exposure to nicotine-containing e-cigarettes affects childhood respiratory health, creating uncertainty about their safety and potential role in increasing asthma risk.

PICOT Question: In Children, how does fetal exposure to nicotine-containing e-cigarettes, compared to no exposure to any form of e-cigarettes, influence the child's risk of developing asthma?

1st Author, et al., Year	**LOE**	**Aim/Purpose**	**Design/ Methods**	**Sample and Setting**	**Variables Studied**	**Instruments and/or Interventions**	**Data Analysis Methods**	**Results /Findings**	**Strengths/ Limitations**	**Overall, Strength / Quality of the Article/ Study**	**Support of PICO(T)**
Krist et al., 2021	Level I	Update USPSTF recommendations on benefits/harms of behavioral, pharmacologic, and e-cigarette interventions for tobacco	USPSTF evidence review of multiple SRs and RCTs on cessation interventions in primary care.	Adults ≥18 (including pregnant persons) in outpatient and hospital settings. Evidence base: ~20 SRs of behavioral interventions (~830 RCTs, >500k participants); SRs of	**IV:** Behavioral counseling, NRT, bupropion, varenicline, e-cig use. **DV:** Smoking cessation rates, perinatal outcomes, harms.	Behavioral interventions: advice, individual/group counseling, quit-lines, mobile-based interventions. Pharmacotherapy: NRT (all forms), bupropion SR, varenicline.)	Pooled RRs and 95% CIs from SRs of RCTs (e.g., physician advice RR 1.76; group counseling RR 1.88; phone and mobile interventions RR ~1.25–1.54).	Behavioral counseling and FDA-approved pharmacotherapy alone or combined ↑ cessation in nonpregnant adults. In pregnant persons, behavioral counseling improves	**Strengths:** Massive Level I evidence; transparent synthesis; clinically actionable recommendations. **Limits:** Insufficient, low-quality data on e-cigs in pregnancy;	**High**	Indirect support: shows e-cig safety/efficacy in pregnancy is uncertain, reinforcing the need to avoid fetal nicotine exposure and supporting the

		cessation in adults, including pregnant persons.		pharmacotherapy; limited e-cig trial data.				cessation and some perinatal outcomes. Evidence for pharmacotherapy and e-cigs in pregnancy is insufficient.	focus is cessation, not child outcomes.		rationale for our PICO.
Agache et al., 2024	Level II	Synthesize evidence on ETS (including e-cigs) and risk of asthma, wheeze, lung function, and asthma outcomes to inform EAACI guidelines.	Systematic review & meta-analysis (PRISMA). Included RCTs and longitudinal cohort studies from MEDLINE/EMBASE.	67 studies (Q1: prenatal/postnatal ETS, mostly healthy children); 24 (Q2: asthma + ETS); 25 (Q3: active smoking in asthma); n ranges 101–844,003 across global cohorts.	**IV:** Prenatal, postnatal, and active exposure to tobacco smoke/e-cigs. **DV:** New-onset asthma, recurrent wheezing, lung function (FEV_1), exacerbations, asthma control, QoL.	ROB tools: Cochrane RoB for RCTs, ROBINS-E for non-RCTs; GRADE for certainty of evidence.	DerSimonian–Laird random-effects MA; OR/RR for categorical outcomes; MD/SMD for continuous; heterogeneity via Q and I^2; $p<0.05$.	Prenatal ETS ↑ asthma (OR 1.28, 95% CI 1.18–1.39) and ↑ recurrent wheeze (OR 1.43, 95% CI 1.30–1.56). Postnatal ETS ↑ asthma (OR 1.12) and ↑ wheeze (OR 1.15). Combined prenatal+postnatal ETS OR 1.49 for asthma. Active smoking worsens asthma	**Strengths:** Rigorous SR/MA; guideline-grade methods (PRISMA, GRADE); clear separation of prenatal/postnatal/active exposure. **Limits:** English-only; primarily observational data; heterogeneity and residual confounding.	**High**	Strong support: demonstrates that prenatal ETS (including e-cigs where studied) increases pediatric asthma and wheezing risk, aligning with fetal nicotine exposure → later asthma pathway.

								control/exacerbations (moderate certainty).			
Deprato, A. et al., 2025	Level II	Quantify association between prenatal vaping and adverse maternal and neonatal outcomes.	Systematic review and meta-analysis (PRISMA; PROSPERO-registered).	25 studies; n=924,376 total; n=7,552 vaping-only pregnancies. Data mostly from large registries (e.g., PRAMS, PATH, national datasets).	**IV:** Vaping during pregnancy (nicotine e-cigs). **DV:** Adverse maternal outcomes and neonatal outcomes (LBW, PTB, SGA, etc.).	Self-report survey data + medical/registry outcomes; ROBINS-type bias assessment; GRADE for certainty.	Random-effects MA of adjusted ORs; heterogeneity via I^2; publication bias via Egger/Begg; $p<0.05$.	Prenatal vaping ↑ odds of adverse neonatal outcome overall (OR 1.53, 95% CI 1.34–1.76). LBW OR 1.56; PTB OR 1.49; SGA OR 1.48.	**Strengths:** Very large, pooled sample; preregistered; consistent associations across multiple outcomes. **Limits:** All observational; self-reported vaping; limited non-US data; no direct long-term respiratory follow-up.	**High** -	Strong **indirect** support: fetal exposure to nicotine-containing e-cigs is linked to LBW, PTB, SGA—well-known risk factors for later childhood asthma and impaired lung development.
Wang et al., 2024	Level II	Test causal relationship between maternal smoking around birth and adult	Two-sample Mendelian randomization using GWAS summary data.	European GWAS datasets; 494,132 participants. Offspring outcomes from FinnGen and UK Biobank.	**IV:** Genetically predicted maternal smoking around birth. **DV:** Asthma, COPD,	Genetic instruments: SNPs linked to maternal smoking; sensitivity tests (MR-Egger, weighted median, MR-PRESSO).	IVW as primary estimator; MR-Egger, weighted median/mode as sensitivity; heterogeneity via	Maternal smoking causally ↑ adult offspring asthma (OR 1.34, 95% CI 1.16–1.54), COPD (OR 1.74), and	**Strengths:** Causal framework reduces confounding; large GWAS datasets; multiple robustness checks.	**High**	Strong mechanistic support reinforces that intrauterine tobacco exposure (and thus

		offspring chronic respiratory diseases.			respiratory insufficiency, emphysema, IPF, and lung cancer.		Cochran's Q; pleiotropy screening.	respiratory insufficiency (OR 2.41) after removing offspring smoking SNPs.	**Limits:** European-only; no timing/dose detail; MR assumptions (pleiotropy) always a concern.		nicotine) has a causal link to chronic respiratory disease, including asthma, across the life course.
Sunde et al., 2021	Level IV	Examine the effect of prenatal tobacco exposure and 17q12–21 genotype on asthma, lung function, and allergy outcomes in early childhood.	Prospective birth cohort (COPSAC2000) with a 7-year follow-up.	n=411 children born to mothers with asthma; ≥36 weeks; no major anomalies; in Denmark.	**IV:** Maternal smoking in 3rd trimester; cotinine (DBS); hair nicotine at 1 year. **DV:** Asthma diagnosis, exacerbations, LRTIs, spirometry, bronchial responsiveness, allergy markers, and atopic dermatitis.	Standardized clinical assessments: GINA-based asthma diagnosis; spirometry/plethysmography; methacholine challenge; SPT; FeNO; eosinophils; EPX; genotyping for rs7216389.	Cox regression for time-to-event (asthma, exacerbations); linear/logistic regression and quasi-Poisson for counts; adjusted for key covariates; $p<0.05$.	Prenatal tobacco exposure doubled asthma risk (aHR 2.05); tripled exacerbations (aHR 3.76); ↑ LRTIs (aIRR 1.87); ↓ FEV_1 and MMEF; ↑ bronchial responsiveness. No association with allergy/type 2 inflammation. Effect on asthma only	**Strengths:** Deep phenotyping; objective lung function and biomarkers; gene–environment analysis. **Limits:** Modest sample; high-risk (maternal asthma) cohort; some self-reported exposure; limited generalizability.	**Moderate**	Direct support: shows that prenatal tobacco exposure alone (nicotine + smoke) is sufficient to increase asthma, exacerbation, and lung function impairment in childhood via structural, not allergic, mechanisms.

								in children without 17q12–21 risk allele.			
Galbo et al., 2022, Cureus	Level IV	Assess the association between prenatal e-cigarette use and unfavorable birth outcomes using PRAMS Phase 8 data (2016–2017).	Retrospective cohort using secondary PRAMS survey data.	N= 71,940 postpartum women 859 reported e-cigarette use	**IV:** E-cigarette use during pregnancy. **DV:** Unfavorable birth outcomes (low birth weight, preterm birth, prolonged hospital stay).	PRAMS Phase 8 survey from 216 and 2017 Birth outcomes from linked vital records	Weighted analyses; t-tests/χ^2 tests for group differences; multivariate logistic regression controlling for confounders; ORs with 95% CI.	Odds of unfavorable birth outcomes 62% higher in women who used e-cigarettes during pregnancy (aOR 1.62, 95% CI: 1.16-2.26, p-value 0.005)	**Strengths:** Large national dataset; standardized PRAMS methodology; multivariable adjustment. **Limitations:** Self-reported exposure (recall + nonresponse bias); e-cig use measured only in the last 3 months; no data on tobacco, alcohol, or drug use; low prevalence of e-cig-users; limited granularity on vaping	**Medium-High**	Partial support: shows prenatal e-cig exposure is associated with adverse birth outcomes linked to impaired fetal development but does **not** directly assess respiratory or asthma outcomes.

									frequency/dose.		
Froggatt et al., 2021	Level VI	Explore postpartum women's perceptions of risks of cigarette and e-cigarette use during pregnancy.	Exploratory qualitative study with semi-structured interviews; thematic analysis using Braun & Clarke.	n=14 postpartum women in NE England who smoked during pregnancy; mean age ~26; mix of light/heavy smokers; all received babyClear© intervention.	Perceived risk of smoking vs vaping in pregnancy; justifications, beliefs, and attitudes.	Semi-structured interviews; transcripts analyzed in NVivo; inductive thematic analysis with double-coding and discussion.	Inductive thematic analysis; no quantitative stats.	Women justified smoking via beliefs and context; many viewed e-cigs as more risky/ "unknown" than cigarettes despite using them; themes: justification /health (cigs) and unknown/experience/comparison/product/advice/ "healthier option" (e-cigs).	**Strengths:** Clear qualitative methods; Braun & Clarke framework; transparent reporting; rich description **Limits:** Small, localized sample; only smokers (no exclusive vapers or non-smokers); not generalizable.	**High**	Indirect-behavioral support: does not answer asthma outcome directly but shows pregnant smokers often misunderstand e-cig risks, which influences fetal exposure patterns we are studying.
Ozeki n et al., 2023	Level VII Basic science/	Determine whether maternal exposure to nicotine-	In vivo mouse experiment with controlled	n= 9 dams (3 exposed, 3 control) n= 41 pups	**IV:** Maternal exposure to nicotine vapor vs room air.	Teague-TE2 vaping system; nicotine confirmed by ELISA; H&E lung histology; ImageJ morphometry;	Group comparisons via t-tests ($p<0.05$); RNAseq using log_2 fold	Nicotine-vape exposure = smaller litters, fetal growth	**Strengths:** Direct experimental control of exposure; robust	**Medium**	Supports: Demonstrates that fetal exposure to nicotine-containing

	animal	containing e-cigs affects fetal lung and skeletal development and underlying gene pathways.	vaping exposure.		**DV:** Litter size, fetal growth, lung structure, ciliated cell differentiation, skeletal measurements, gene expression.	skeletal staining; whole-transcriptome RNAseq.	change and FDR thresholds.	restriction, reduced lung airspace, impaired ciliated cell differentiation, altered developmental pathways (Wnt, BMP/TGF-β, Notch, Hedgehog), and shorter craniofacial/ long bones, especially in Kcnj2 mutants.	developmental assays; coherent biological story. **Limits:** Small animal sample; mouse model; exposure levels not identical to human vaping patterns.		e-cig vapor structurally disrupts lung development, increasing later asthma risk in human offspring.

References

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Synthesis Table

Problem Statement: Limited evidence exists on how fetal exposure to nicotine-containing e-cigarettes affects childhood respiratory health, creating uncertainty about their safety and potential role in increasing asthma risk. **PICO(T) Question: In** children, how does fetal exposure to nicotine-containing e-cigarettes, compared to no exposure to any form of e-cigarettes, influence the child's risk of developing asthma?

Studies	Design	Interventions	Sample	Outcome(s)	Alignment to PICO ↑↓→
Agache et al., 2024	SR/MA (Level II)	Prenatal, postnatal, and active exposure to tobacco/e-cigs vs none	116 studies (>800,000 participants)	Prenatal ETS ↑ asthma; ↑ recurrent wheeze	↑ Supports PICO
Wang et al., 2024	Mendelian randomization (Level II)	Genetic instruments for maternal smoking around birth	494,132 participants	Maternal smoking ↑ offspring asthma risk	↑ Supports PICO
Sunde et al., (2021)	Longitudinal cohort (Level II)	Prenatal tobacco exposure	n = 411	↑ Asthma, exacerbations; ↓ FEV_1	↑ Direct support
Galbo et al., 2022	Retrospective Cohort Study (Level IV)	Pregnancy Risk Assessment Monitoring System (PRAMS) Phase 8 core survey between 2016-2017	n = 71,940 postpartum women	↑ unfavorable birth outcomes	→ Partial alignment
Froggatt et al., 2021	Qualitative (Level VI)	Maternal perceptions of smoking vs vaping risk	n = 14 postpartum women	E-cigs viewed as risky/unknown; smoking justified	→ Partial alignment
Krist et al., 2021	SR (Level I)	Smoking-cessation interventions	>500,000 participants	Behavioral counseling effective; e-cig evidence insufficient	→ Partial alignment
Ozekin et al., 2023	Animal experiment (Level V)	Maternal vaping exposure in mice	n= 9 dams n= 41 pups	Impaired lung development; growth restriction	→ neutral
Deprato, A. et al., 2025	SR/MA (Level I)	Prenatal vaping exposure	25 studies n= 924,376	↑ Adverse neonatal outcomes (LBW, PTB, SGA)	→ Indirect support

Adapted from: Melnyk, B.M. & Fineout-Overholt, E. (2023). Evidence-based practice in nursing & healthcare: A guide to best practice (4th ed., p. 726). Wolters Kluwer.