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Review Article

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Systematic Review: The Persistent Association Between Infant Antibiotic Exposure and Childhood Asthma After Accounting for Confounding by Indication and Reverse Causation

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Abstract

Background: Early-life antibiotic exposure has been repeatedly associated with an increased risk of childhood asthma. However, this association is vulnerable to substantial methodological bias, particularly Confounding by Indication (CbI) and Reverse Causation (RC). This systematic review evaluates whether the association persists in studies employing advanced epidemiologic methods designed to mitigate these biases.

Methods: A systematic search of PubMed, Embase, Web of Science and the Cochrane Library was conducted from January 2010 through December 11, 2025. Eligible publications included (1) primary observational studies (cohort or case-control designs) evaluating antibiotic exposure during infancy (0–24 months) and physician-diagnosed asthma at ≥4 years and/or (2) systematic reviews/meta-analyses that explicitly evaluated or stratified results by approaches addressing CbI and/or RC (e.g., adjustment for respiratory tract infections, exclusion of early wheezing, or comparable bias-mitigation strategies). Study selection followed PRISMA 2020 guidelines. Methodological quality was assessed using the Newcastle–Ottawa Scale for primary studies; systematic reviews were assessed narratively for relevance to the review objective.

Results: Four eligible studies were included. Crude observational estimates reported in meta-analytic syntheses demonstrated a strong association (pooled OR ≈1.37). In analyses explicitly addressing CbI and RC, estimates attenuated but remained statistically significant (pooled OR 1.19; 95% CI, 1.11–1.28). In contrast, a nationwide sibling-matched cohort study eliminated the association for fetal exposures and non-respiratory indications, suggesting substantial familial confounding. A persistent association remained only for antibiotics prescribed for respiratory infections (sibling-matched HR 2.36), consistent with residual confounding by illness severity.

Conclusion: The association between infant antibiotic exposure and childhood asthma is largely explained by shared familial factors and residual confounding related to respiratory illness severity rather than a direct causal effect of antibiotics. While biological plausibility via gut microbiome disruption remains, current epidemiologic evidence does not provide strong support for a direct causal relationship. Further studies using advanced causal inference methods are warranted.

Keywords: Antibiotics, Asthma, Infancy, Confounding by indication, Reverse causation, Sibling analysis, Epidemiology

Introduction

Childhood asthma is one of the most prevalent chronic pediatric conditions worldwide and arises from a complex interplay between genetic susceptibility and environmental exposures. Observational studies have repeatedly reported positive associations between antibiotic exposure in infancy and subsequent childhood asthma, prompting hypotheses that microbiome disruption during immune development may contribute to asthma pathogenesis. However, causal interpretation is complicated by two major biases: Confounding by indication, where antibiotics are prescribed for Respiratory Tract Infections (RTIs) that independently increase asthma risk and reverse causation, where early asthma symptoms are misdiagnosed as infection and treated with antibiotics.

This systematic review focuses on evidence that explicitly addresses these biases using advanced epidemiologic strategies, including sibling-matched designs and analyses adjusting for RTIs or excluding early wheezing.

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Methods

Search Strategy

A systematic literature search was conducted in PubMed, Embase, Web of Science and the Cochrane Library for studies published between January 2010 and December 11, 2025. Search terms included combinations of antibiotics, infant, early life, childhood asthma, confounding by indication, reverse causation and sibling analysis. Reference lists of eligible studies and relevant reviews were manually screened.

Eligibility criteria

Eligible publications included:

1. Primary observational studies (cohort or case-control) evaluating antibiotic exposure during infancy (0–24 months) and reporting physician-diagnosed asthma at ≥4 years with explicit strategies to mitigate CbI and/or RC, including sibling-matched designs, exclusion of early wheezing, or explicit adjustment for respiratory tract infections; and/or
2. Systematic reviews/meta-analyses that explicitly evaluated the impact of CbI and/or RC mitigation (e.g., subgroup analyses restricted to studies addressing these biases).

Publications were excluded if they: (1) assessed asthma prior to age 4 as the primary outcome, (2) did not distinguish timing of antibiotic exposure in infancy, or (3) did not evaluate or stratify findings by approaches addressing CbI/RC.

Study selection

Two reviewers screened titles/abstracts and full texts. Disagreements were resolved by consensus. Study selection is summarized in the PRISMA 2020 flow diagram (Figure 1).

Data extraction

Extracted data included study design, population characteristics, exposure definition, asthma outcome definition, bias-mitigation methods (CbI/RC) and effect estimates (OR/HR) with confidence intervals.

Quality assessment

Primary observational studies were assessed using the Newcastle–Ottawa Scale. Systematic reviews/meta-analyses were assessed narratively for alignment with the objective and transparency of subgroup/sensitivity analyses addressing CbI/RC.

Data synthesis

Due to heterogeneity in study designs and analytical strategies, a narrative synthesis was performed, emphasizing comparisons between crude estimates, bias-adjusted meta-analytic estimates and sibling-controlled analyses. Pooled effect estimates reported in the Results were extracted from previously published meta-analyses and were not recalculated in the present review.

Results

Study Characteristics

Four eligible publications were included in the final synthesis (Table 1). Study selection is summarized in the PRISMA 2020 flow diagram (Figure 1).

Study	Country	Design	Sample size	Exposure definition	Asthma outcome definition	CbI/RC mitigation approach	Key findings / notes
Zhang et al. [1]	Multi-country	Meta-analysis	>1,000,000 (combined)	Antibiotic exposure in infancy (varied across included studies)	Asthma assessed ≥4 years (study-dependent)	Subgroup analyses of studies addressing CbI/RC	Crude OR 1.37; bias-mitigated subgroup OR 1.19.
Örtqvist et al. [2]	Sweden	Population-based cohort + sibling-matched	1.8 million	Fetal and early-life antibiotics; indication-stratified	Childhood asthma	Sibling matching; infection-related controls	Association eliminated for fetal/non-respiratory; persistent for respiratory indications (HR 2.36).
Penders et al. [3]	Netherlands	Systematic review/meta-analysis	22 studies	Infant antibiotic exposure	Wheeze/asthma (varied); asthma commonly ≥5 yrs	Infection adjustment in included studies	Provides contextual pooled evidence; susceptibility to residual confounding acknowledged.
Lu et al. [4]	China	Systematic review/meta-analysis	34 studies	Early-life antibiotic exposure	Childhood asthma (commonly ≥5 yrs)	Adjusted analyses for RTIs/early wheeze	Attenuated but persistent association after adjustment.

Table 1: Characteristics of Included Studies. Note: Table includes both primary observational studies and systematic reviews/meta-analyses that explicitly addressed confounding by indication and/or reverse causation.

Flow diagram summarizing identification, screening, eligibility assessment and inclusion of studies in the systematic review. A total of 15,420 records were identified through database searching. After removal of 5,550 duplicates, 9,870 records were screened by title and abstract; 9,800 were excluded. Seventy full-text articles were assessed for eligibility; 66 were excluded based on predefined criteria. Four studies met inclusion criteria and were included in the final synthesis.

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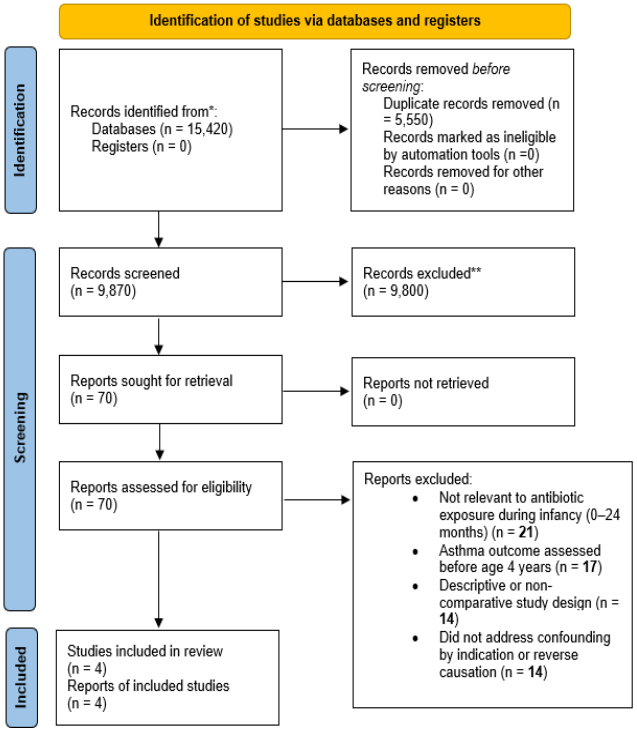

Figure 1: PRISMA 2020 flow diagram.

Evidence from meta-analyses addressing CbI and RC

Zhang et al., reported a pooled crude association (OR 1.37; 95% CI, 1.29–1.45) and demonstrated attenuation in analyses of studies that adjusted for CbI and RC (OR 1.19; 95% CI, 1.11–1.28) [1]. Lu et al., similarly reported an attenuated but persistent association after bias adjustment in included studies [4].

Evidence from sibling-matched designs

Örtqvist et al., employed a nationwide sibling-matched cohort design [2]. Associations observed in conventional cohort analyses for fetal exposure and non-respiratory indications were eliminated in sibling comparisons (fetal exposure HR ≈0.99; non-respiratory indication HR ≈0.85). In contrast, antibiotic exposure for respiratory indications remained associated with asthma in sibling analyses (HR 2.36), consistent with residual confounding by severity or type of underlying respiratory illness.

Discussion

This review indicates that much of the reported association between infant antibiotic exposure and childhood asthma is likely explained by confounding and reverse causation. Meta-analytic estimates attenuate when studies account for these biases, suggesting that crude associations overestimate any true effect. The strongest evidence comes from sibling-matched analyses demonstrating that familial confounding explains associations for fetal exposure and non-respiratory indications. The remaining association observed for respiratory-indication antibiotics likely reflects residual confounding by infection severity rather than a direct antibiotic effect.

Although antibiotic-driven microbiome disruption remains biologically plausible, current epidemiologic evidence does not strongly support a causal relationship. Future research should prioritize designs and analyses that more directly address unmeasured confounding and infection severity, including causal inference frameworks and longitudinal microbiome studies.

Contextual note (not included in synthesis): Okubo et al. (2021) evaluated antibiotic treatment during hospitalization for asthma exacerbation and was not included because it did not assess infant exposure (0–24 months) leading to incident asthma at ≥4 years.

Limitations

This review is limited by heterogeneity across included studies in exposure ascertainment, asthma diagnostic criteria and the operationalization of bias-mitigation strategies. Publication bias is possible. Sibling-matched designs cannot account for non-shared factors such as individual-level differences in infection severity. Additionally, relatively few studies apply advanced causal inference methods, limiting definitive causal conclusions.

Conclusion

The association between infant antibiotic exposure and childhood asthma is largely attributable to shared familial factors and residual confounding by respiratory illness severity. Evidence for a direct causal effect is limited. Rigorous causal inference studies are needed to clarify remaining uncertainties and to test microbiome-mediated mechanisms.

Competing Interests

The authors declare no conflict of interests for this article.

References

1. Zhang Z, Wang J, Wang H, Li Y, Jia Y, et al. (2021) Association of infant antibiotic exposure and risk of childhood asthma: a meta-analysis. World Allergy Organ J 14(11): 100607.
2. Örtqvist AK, Lundholm C, Kieler H, Ludvigsson JF, Fall T, et al. (2014) Antibiotics in fetal and early life and subsequent childhood asthma: nationwide population-based study with sibling analysis. BMJ 349: g6979.
3. Penders J, Vink C, Driessen GJ, London N, Thijs C, et al. (2011) Infant antibiotic use and wheeze and asthma risk: A systematic review and meta-analysis. Eur Respir J 38(2): 295-302.
4. Lu Y, Li Z, Zhang Y (2023) Early-life antibiotic exposure and childhood asthma: A systematic review and meta-analysis. Pediatr Pulmonol 58(3): 1010-1020.