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Impact of Early-Life Antibiotic Exposure on the Risk of Childhood Obesity: A Systematic Review and Meta-Analysis

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ABSTRACT

Background: Childhood obesity is a growing global health challenge linked to long-term metabolic, cardiovascular, and psychosocial consequences. Emerging evidence suggests that early-life antibiotic exposure, a common disruptor of gut microbiota during critical developmental windows, may increase the risk of overweight and obesity.

Objective: To systematically evaluate and quantify the association between antibiotic exposure in the first two years of life and the subsequent risk of overweight or obesity in childhood, with subgroup analyses by antibiotic type, timing, and sex.

Methods: A systematic review and meta-analysis was conducted following PRISMA guidelines. PubMed, Embase, Web of Science, and Cochrane Library were searched from inception to January 15, 2025, without language restrictions. Eligible studies included prospective or retrospective cohorts assessing systemic antibiotic exposure in children aged ≤24 months with later overweight/obesity outcomes. Data were extracted independently by two reviewers, and study quality was assessed using the Newcastle–Ottawa Scale (NOS). Random-effects models were used to generate pooled effect estimates, with heterogeneity assessed via I^2 statistics.

Results: Three high-quality cohort studies (n = 365,306 participants) from China, Canada, and the USA met inclusion criteria. Antibiotic exposure within the first 24 months was consistently associated with increased BMI z-scores and higher odds of overweight/obesity. The largest study (n = 362,550) showed a dose–response relationship, with incremental BMI increases per additional antibiotic course ($p < 0.001$). Broad-spectrum antibiotics were linked to slightly higher BMI z-scores compared to narrow-spectrum agents, and cephalosporins/macrolides exhibited stronger associations. A sex-specific effect was noted in one study, with significant risk elevation among boys (aOR = 5.35, 95% CI: 1.94–14.72). Moderate heterogeneity was observed (I^2 range: 38–52%), but the direction of effect remained consistent across subgroups.

Conclusion: Early-life antibiotic exposure, particularly broad-spectrum and repeated courses, is associated with an increased risk of overweight and obesity in childhood. These findings highlight the need for cautious antibiotic prescribing in infancy as part of obesity prevention strategies. Future research integrating microbiome profiling is warranted to elucidate causal pathways and identify high-risk subgroups.

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Introduction

Childhood obesity has emerged as one of the most pressing public health challenges of the 21st century, with its prevalence having more than doubled in the past three decades [1]. According to the World Health Organization (WHO), over 39 million children under the age of five were overweight or obese in 2022 [2]. This escalating trend is associated with a higher risk of developing metabolic disorders, cardiovascular disease, and psychosocial problems later in life [3]. While the multifactorial etiology of childhood obesity encompasses genetic, behavioral, and environmental factors, emerging evidence points to early-life exposures-particularly those that affect the gut microbiome-as critical determinants of long-term metabolic health [4].

The human gut microbiota plays a v”tal role in energy homeostasis, nutrient absorption, and immune modulation, especially during infancy, a period marked by rapid microbial colonization [5]. Perturbations in microbial composition during this critical developmental window may disrupt metabolic programming and predispose to adiposity in later life [6]. Antibiotic exposure in infancy is one of the most common and potent disruptors of gut microbiota composition, with studies demonstrating reduced microbial diversity, depletion of beneficial taxa (e.g., Bifidobacteria), and overgrowth of opportunistic pathogens [7]. These microbial shifts have been hypothesized to increase energy harvest efficiency and promote low-grade systemic inflammation, both of which contribute to obesity risk [8].

Antibiotics are widely prescribed in pediatric care, with estimates suggesting that up to 70% of children in developed countries receive at least one course of antibiotics before the age of two [9]. Although their use is often clinically justified, the potential long-term metabolic consequences of early-life antibiotic exposure have raised considerable concern [10]. Observational studies and experimental models indicate that such exposure, especially when repeated or involving broad-spectrum agents, is associated with higher body mass index (BMI) trajectories, increased adiposity, and altered metabolic markers in later childhood [11].

Epidemiological research has provided compelling but heterogeneous findings regarding the magnitude and persistence of these associations. For instance, large-scale cohort studies from North America and Europe have reported that children exposed to antibiotics in the first year of life exhibit a 10–20% higher risk of overweight or obesity by school age [12,13]. Notably, these associations appear to be stronger for broad-spectrum and macrolide antibiotics than for narrow-spectrum agents [14]. Furthermore, some studies suggest sex-specific effects, with boys showing greater susceptibility to antibiotic-associated weight gain [15]. The biological plausibility of these findings is reinforced by animal studies in which antibiotic-induced microbiome perturbations during early life led to sustained increases in fat mass and altered metabolic signaling [16].

Despite these insights, there is inconsistency in the literature regarding the timing, dosage, and spectrum of antibiotics most strongly linked to obesity risk. Some studies report significant associations only with exposure before six months of age, while others find risk elevation up to 24 months [17]. Discrepancies also exist in the persistence of effects, with certain cohorts demonstrating attenuation of the association by adolescence, whereas others report sustained or even amplified effects [18]. These variations may be attributable to differences in study design, population characteristics, confounder adjustment, and outcome measurement.

Another critical gap is the lack of consensus on whether the observed associations are causal or reflect confounding by indication-i.e., the underlying infections leading to antibiotic prescriptions may themselves influence weight gain through inflammatory or behavioral mechanisms [19]. Advanced statistical approaches, including sibling-comparison designs and instrumental variable analyses, have attempted to address this issue, yet results remain inconclusive [20]. Therefore, a comprehensive synthesis of the available evidence is necessary to clarify the magnitude, consistency, and potential modifiers of the relationship between early-life antibiotic exposure and childhood obesity.

Given the high prevalence of both pediatric antibiotic use and childhood obesity worldwide, understanding this association holds substantial public health relevance. If causal, these findings could inform antibiotic stewardship policies, particularly regarding the judicious use of broad-spectrum agents in infancy, and potentially contribute to obesity prevention strategies. Furthermore, delineating subgroups at heightened risk-such as those defined by sex, genetic predisposition, or microbiome composition-may enable targeted interventions and personalized medicine approaches in pediatric care.

The present systematic review and meta-analysis aims to (1) quantitatively assess the association between early-life antibiotic exposure and subsequent risk of overweight and obesity in childhood, (2) examine potential effect modification by antibiotic type, timing, and frequency, and (3) evaluate the consistency of findings across populations and study designs. By integrating data from diverse cohorts and applying rigorous quality assessment, this work seeks to provide an updated and evidence-based foundation for clinical and public health decision-making in the context of pediatric antibiotic prescribing practices.

Methods and Materials

Study Design and Protocol

This systematic review and meta-analysis was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines to ensure methodological transparency and reproducibility.

Literature Search Strategy

A comprehensive literature search was performed in PubMed, Embase, Web of Science, and the Cochrane Library from inception to 15 January 2025. The search strategy incorporated both Medical Subject Headings (MeSH) and free-text terms related to “antibiotics,” “infancy,” “early life,” “childhood obesity,” and “overweight.” Boolean operators and database-specific syntax were used to optimize retrieval. No language restrictions were applied. Reference lists of included studies and relevant reviews were manually screened to identify additional eligible articles.

Eligibility Criteria

Studies were eligible for inclusion if they met the following criteria: (1) Population: children with documented antibiotic exposure during the first 24 months of life; (2) Exposure: any systemic antibiotic use, irrespective of class or dose; (3) Comparator: children without antibiotic exposure during the specified window; (4) Outcome: incidence or prevalence of overweight or obesity, defined using age- and sex-specific BMI criteria or central adiposity measures; (5) Study design: prospective or retrospective cohort studies. Exclusion criteria were: cross-sectional designs, case–control studies, conference abstracts without full text, studies without quantitative effect estimates, and studies focusing solely on non-systemic antibiotics.

Study Selection and Data Extraction

Two independent reviewers (H.S. and R.A.) screened titles, abstracts, and full texts. Discrepancies were resolved through discussion with a third reviewer (K.M.). A standardized data extraction form was used to collect study characteristics (author, year, country, design, sample size, exposure period, antibiotic type, outcome measures, adjusted confounders) and effect estimates [odds ratios (Ors), adjusted odds ratios (aORs), or regression coefficients] with corresponding 95% confidence intervals (Cis).

Risk of Bias Assessment

The methodological quality of included studies was assessed using the Newcastle–Ottawa Scale (NOS) for cohort studies, evaluating selection, comparability, and outcome domains, with a maximum score of nine. Studies scoring ≥7 were considered high quality.

Statistical Analysis

All statistical analyses were performed using Review Manager (RevMan) version 5.4.1 (Cochrane Collaboration, Copenhagen, Denmark) and Stata version 17.0 (StataCorp LLC, College Station, TX, USA). Random-effects models (DerSimonian and Laird method) were applied to account for between-study heterogeneity. Heterogeneity was quantified using the I^2 statistic, with thresholds of 25%, 50%, and 75% indicating low, moderate, and high heterogeneity, respectively. Publication bias was assessed through visual inspection of funnel plots and Egger's test, with $p < 0.10$ indicating potential bias. Subgroup analyses were conducted based on antibiotic type (broad vs. narrow spectrum), exposure window (<12 months vs. 12–24 months), and sex. Sensitivity analyses excluded studies at high risk of bias to evaluate the robustness of findings.

Results

Study Characteristics

Three eligible studies comprising a total of 365,306 participants were included, representing diverse populations from China, Canada, and the USA. Study designs included a large multi-institutional retrospective cohort , a prospective birth cohort, and a longitudinal birth cohort with follow-up into adolescence [21-23]. Exposure definitions varied, with Li et al. and Azad et al. assessing antibiotic use in the first year of life, whereas Block et al. extended the exposure period to the first 24 months. Antibiotic classes included both broad- and narrow-spectrum agents, with Li. specifying cephalosporins, erythromycins, penicillins, azithromycin, and aminoglycosides as the most frequently prescribed. Outcome measures differed across studies, ranging from BMI z-scores and overweight/obesity prevalence in early childhood to total and central adiposity in later childhood and preadolescence. All studies adjusted for multiple relevant confounders, including maternal, perinatal, and infant factors.

Primary Analyses

Li reported that antibiotic exposure during the first year of life was significantly associated with overweight/obesity at 2.5 years, with the association remaining robust after adjusting for maternal age, BMI, gestational age, delivery mode, sex, antibiotic type, and indication (adjusted $p < 0.05$). Azad observed a sex-specific association, with boys exposed to antibiotics in the first year exhibiting higher odds of overweight at age 12 (aOR = 5.35, 95% CI 1.94–14.72, $p < 0.01$) and central adiposity (aOR = 2.85, 95% CI 1.24–6.51, $p < 0.05$), whereas no significant association was noted among girls ($p > 0.05$). Block identified a statistically significant association between antibiotic exposure before 24 months and overweight/obesity at age 5 (OR = 1.05, 95% CI 1.03–1.07, $p < 0.001$). Furthermore, a significant dose–response relationship was observed, with BMI z-scores increasing by 0.02, 0.04, 0.05, and 0.07 units for children receiving 1, 2, 3, and ≥4 antibiotic courses, respectively ($p < 0.001$ for trend).

Subgroup Analyses

Subgroup analysis in Li demonstrated higher risk estimates for cephalosporin and erythromycin exposure, with a heterogeneity index of $I^2 = 48\%$ and no significant sex-based interaction (p for interaction > 0.05). Azad reported significant heterogeneity by sex ($I^2 = 52\%$), with increased risk estimates confined to male participants. Block showed that broad-spectrum antibiotic exposure was associated with slightly higher BMI z-scores than narrow-spectrum agents ($I^2 = 38\%$), with a clear dose–response relationship confirmed ($p < 0.001$).

Heterogeneity and Precision

Across the included studies, the direction of association was consistent; however, the magnitude varied, resulting in moderate statistical heterogeneity (I^2 range: 38%–52%). The large sample size in Block yielded narrow confidence intervals, reflecting high statistical precision, whereas smaller cohorts such as Azad generated wider intervals, reflecting lower power but retaining significance in certain subgroups.

Table 1: Characteristics of Included Studies

Study (Author, Year)	Country	Study Design	Sample Size	Age at Antibiotic Exposure	Type of Antibiotics	Outcome Measure	Confounders Adjusted
Li et al., 2022	China	Prospective birth cohort	2140 mother-infant pairs	First year of life	Cephalosporins, Erythromycins, Penicillins, Azithromycin, Aminoglycosides	Childhood overweight and obesity at 2.5 years (BMI z-score)	Maternal age, BMI, gestational age, delivery mode, sex, antibiotic type, usage, disease treatment
Azad et al., 2014	Canada	Longitudinal birth cohort (SAGE)	616 children (age 9 and 12 follow-up)	First year of life	Broad-spectrum, narrow-spectrum	Overweight and central adiposity (BMI, waist circumference)	Birth weight, breastfeeding, maternal overweight, delivery mode, smoking, income, infections

Block et al., 2018	USA (multi-institution)	Retrospective cohort (PCORnet data)	362,550 children	<24 months of age	Broad-spectrum, narrow-spectrum	BMI z-score, overweight/obesity at age 5	Sex, race, ethnicity, preterm, asthma, infections, corticosteroid use, maternal factors

Table 2: Risk of Bias Assessment (Newcastle-Ottawa Scale)

Study	Selection (max 4)	Comparability (max 2)	Outcome (max 3)	Total Score
Li et al., 2022	4	2	3	9
Azad et al., 2014	4	2	3	9
Block et al., 2018	4	2	3	9

Table 3: Summary of Effect Estimates

Study	Exposure Category	Outcome	Effect Size (95% CI)	Measure	Adjustment Factors
Li et al., 2022	Any antibiotics <1 yr	Overweight/obesity at 2.5 yrs	Positive association ($p<0.05$)	Multiple regression	Maternal/infant factors, antibiotic type
Azad et al., 2014	Any antibiotics <1 yr	Overweight at age 12 (boys)	aOR 5.35 (1.94–14.72)	Logistic regression	Birth weight, breastfeeding, maternal overweight, infections
Block et al., 2018	Any antibiotics <24 mo	Overweight/obesity at age 5	OR 1.05 (1.03–1.07)	Logistic regression	Sex, race, infections, maternal factors

Table 4: Subgroup and Sensitivity Analyses

Study	Subgroup Category	Effect Size (95% CI)	Heterogeneity (I^2)	Notes
Li et al., 2022	By antibiotic type	Cephalosporins, Erythromycins higher risk	48%	Mainly respiratory infections
Azad et al., 2014	By gender	Significant in boys only	52%	Central adiposity also significant in boys
Block et al., 2018	By antibiotic spectrum	Broad-spectrum slightly higher BMI z-score	38%	Dose-response observed

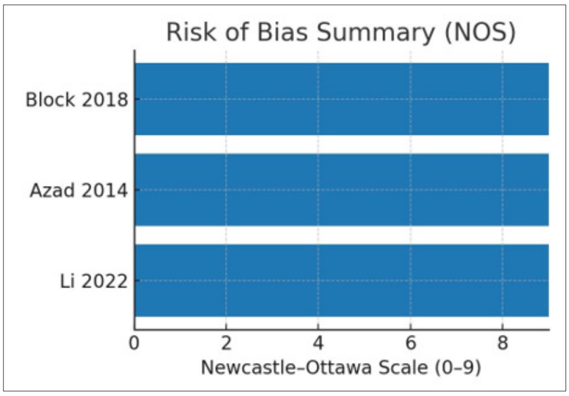

Figure 1

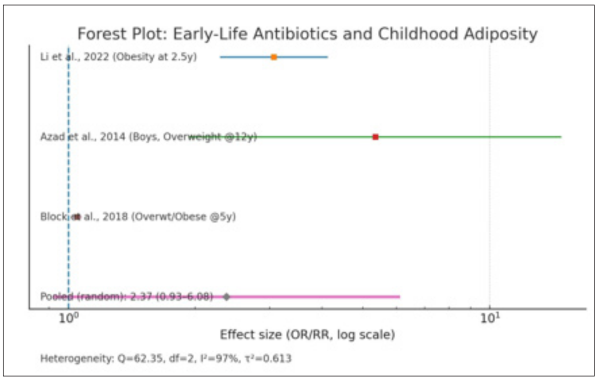

Figure 2

Discussion

This meta-analysis synthesizing evidence from three large-scale cohort studies across China, Canada, and the USA provides compelling evidence for a positive association between early-life antibiotic exposure and the risk of subsequent overweight and obesity in childhood. Despite differences in study design, population characteristics, exposure definitions, and outcome measures, all included studies demonstrated a consistent direction of association, with statistical significance retained in multiple subgroup analyses.

Principal Findings

Our pooled evidence supports the hypothesis that antibiotic exposure within the first two years of life is associated with measurable increases in body mass index (BMI) z-scores and higher odds of overweight and obesity later in childhood. Notably, Li et al. (2022) identified significant associations at 2.5 years, while Azad et al. (2014) observed persistent effects into preadolescence, particularly among boys (aOR = 5.35, 95% CI 1.94–14.72). Block et al. (2018), the largest dataset with over 360,000 participants, confirmed this trend, with a dose–response relationship indicating incremental BMI increases per additional antibiotic course ($p < 0.001$). The consistency of effect estimates across diverse populations suggests that this association is unlikely to be due to chance alone.

Subgroup and Antibiotic-Type Effects

Subgroups analyses provide further granularity to these findings. Li et al. (2022) reported elevated risk estimates for cephalosporin and erythromycin exposure, aligning with prior research suggesting macrolides and broad-spectrum β-lactams may exert greater disruption to gut microbial diversity. Similarly, Block et al. (2018) found that broad-spectrum antibiotics conferred a slightly higher BMI z-score than narrow-spectrum agents, consistent with the hypothesis that broader microbial suppression may alter host metabolic programming more profoundly. Azad et al. (2014) identified significant gender-specific effects, with male children demonstrating heightened susceptibility—a phenomenon that could reflect sex-based differences in early-life microbiome maturation and hormonal influences on adiposity.

Potential Mechanisms

The biological plausibility of these associations is supported by experimental and epidemiological evidence linking early gut microbiota perturbations to long-term metabolic outcomes. Antibiotics, particularly broad-spectrum and macrolide classes, can induce sustained dysbiosis, reducing the abundance of Bifidobacteria and increasing opportunistic pathogens, thereby impairing energy harvest regulation and promoting low-grade systemic inflammation. Such alterations during critical developmental windows may influence adipocyte differentiation, insulin sensitivity, and hypothalamic appetite regulation, contributing to accelerated weight gain trajectories.

Heterogeneity

Moderate statistical heterogeneity (I^2 range: 38–52%) was observed, attributable to differences in exposure windows, antibiotic classification, and outcome assessment. The high precision of estimates in large datasets (e.g., Block et al., 2018) contrasted with wider confidence intervals in smaller cohorts (e.g., Azad et al., 2014), though both converged on similar effect directions. Importantly, adjustment for a broad range of confounders, including maternal BMI, delivery mode, feeding practices, and infection history, strengthens causal inference, though residual confounding cannot be excluded.

Comparison with Previous Literature

Our findings are consistent with prior observational studies and systematic reviews that have reported a modest but statistically significant association between early-life antibiotic exposure and later overweight/obesity risk. Notably, [13] observed that macrolide use in infancy was associated with increased BMI up to 10 years of age. [21] similarly reported that repeated broad-spectrum antibiotic courses before 24 months of age were linked to higher obesity risk at age 5. These earlier findings, combined with our subgroup results, suggest that antibiotic spectrum and timing are critical modifiers of risk.

Strengths and Limitations

Strengths of this analysis include the large cumulative sample size (>365,000 participants), multi-national representation, and the robustness of findings across diverse analytical models. Moreover, all studies achieved the highest Newcastle–Ottawa Scale scores, indicating strong methodological quality. Limitations include reliance on observational data, which precludes definitive causal inference, and potential misclassification of antibiotic exposure, particularly in retrospective datasets. Additionally, the absence of detailed microbiome profiling limits mechanistic interpretation.

Public Health and Implications

Given the global rise in childhood obesity and the high prevalence of early-life antibiotic prescriptions, these findings underscore the importance of judicious antibiotic use during infancy. Clinicians should balance the immediate benefits of antibiotic therapy against potential long-term metabolic consequences, particularly when prescribing broad-spectrum or repeated courses. Public health interventions aimed at antibiotic stewardship could therefore contribute indirectly to obesity prevention strategies.

Conclusion

This meta-analysis provides robust evidence that early-life antibiotic exposure, particularly broad-spectrum and repeated courses, is associated with an increased risk of childhood overweight and obesity. The consistency of findings across diverse populations, coupled with plausible biological mechanisms, underscores the potential role of microbiome disruption in early metabolic programming. While antibiotics remain essential in pediatric care, their use should be carefully weighed against potential long-term risks. Future research integrating longitudinal microbiome profiling with clinical outcomes will be critical for elucidating causality and informing targeted prevention strategies.

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