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REVIEW ARTICLE

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Early-life antibiotic exposure increases the risk of developing allergic symptoms later in life: A meta-analysis

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Abstract

This study systematically reviewed and quantified the relationship between exposure to antibiotics during the first 2 years of life and the risk of allergies/atopies including hay fever, eczema, food allergy, positive skin prick testing (SPT), or elevated allergen-specific serum/plasma immunoglobulin (Ig) E levels later in life. PubMed and Web of Science databases were searched for observational studies published from January 1966 through November 11, 2015. Overall pooled estimates of the odds ratios (ORs) were obtained using fixed or random-effects models. Early-life exposure to antibiotics appears to be related to an increased risk of allergic symptoms of hay fever, eczema, and food allergy later in life. The summary OR for the risk of hay fever (22 studies) was 1.23, 95% confidence interval (CI):1.13-1.34; I^2: 77.0%. The summary OR for the risk of eczema (22 studies) was 1.26, 95% CI: 1.15-1.37; I^2: 74.2%, and the summary OR for food allergy (3 studies) was 1.42, 95% CI: 1.08-1.87; I^2: 80.8%. However, no association was found for antibiotics exposure early in life and objective atopy measurements including positive SPT or elevated allergen-specific serum/plasma IgE levels.

KEYWORDS
allergy, antibiotic, atopy, children, early life

1 | INTRODUCTION

Antibiotics are among the most commonly prescribed medications in children with acute otitis media (AOM) and upper respiratory tract infections (URIs).[1-3] A worldwide study of the use of antibiotics showed a prevalence rate of 57.6% among hospitalized neonates and children.[4] A US study by Hicks et al[5] in an outpatient setting also showed that antibiotics were more prescribed in infants and children ≤2 years of age than in other age groups.

Early-life exposure to antibiotics has been related to some later life morbidities such as obesity, arthritis, asthma, and allergies.[6,7] A meta-analysis from 2006 showed a higher risk of asthma among those children exposed to antibiotics in early childhood.[8] However, a more recent meta-analysis from 2011 reported that the association between antibiotics exposure and subsequent development of wheeze/asthma was weak when the analysis was adjusted for reverse causation and confounding by indication.[9]

Several studies have suggested that early-life exposure to antibiotics is associated with an increased risk of developing allergies and atopies later in life, but results are inconsistent.[10-46] Therefore, the aim of this study was to conduct a systematic review and meta-analysis to assess and quantify the relationship between early-life exposure to antibiotics and the risk of developing symptoms of hay fever, eczema, food allergy, positive skin prick testing (SPT), or elevated allergen-specific serum/plasma immunoglobulin (Ig) E levels later in life.

Abbreviations: CI, confidence interval; HR, hazard ratio; IgE, immunoglobulin E; OR, odds ratio; SPT, skin prick test.

2 | METHODS

For this meta-analysis, we followed the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines.[47]

2.1 | Data source

We conducted a comprehensive literature search of PubMed and the Web of Science using multiple search terms shown in Table S1. Additional articles were retrieved through a manual search of references from included articles.

2.2 | Inclusion and exclusion criteria

Studies were included if (i) they assessed the association between antibiotics consumption during the first 2 years of life and the risk of developing hay fever, eczema, food allergy, positive SPT, or elevated allergen-specific serum/plasma IgE levels, and (ii) a quantified measurement of association between exposure and outcomes was reported as odds ratio (OR) or hazard ratio (HR) or could be calculated as OR.

Our literature search was restricted to studies published in English from January 1966 through November 11, 2015. We excluded those studies that were limited to ever use of antibiotics (not restricted to the first 2 years of life).[44-46]

2.3 | Clinical end points

The outcomes studied in our meta-analysis were as follows: (i) hay fever defined as any experience of allergic rhinitis such as sneezing, runny nose, nasal blockage or red and itching eyes, or any medication used for hay fever or a physician diagnosis of hay fever during the last 12 months. Three studies included children younger than 5 years where only in one study the definition of hay fever was based on hay fever symptoms and allergen-specific sensitization,[36] (ii) eczema defined as any dermatitis, for example, itching skin disease or itchy rash reported by parents or diagnosed by a physician during the last 12 months before outcome measurement, (iii) food allergy defined as any symptoms to food plus specified criteria, for example, clinical examination and a positive SPT or cow's milk allergy (with ICD-10 codes L27.2 or K52.2), (iv) a positive response to SPT, and e) increased serum/plasma specific IgE level (≥0.25 IU/mL or ≥0.3 KU/L).

2.4 | Reporting more than one risk estimate

For studies that reported ≥1 ORs/HRs for the associations between antibiotics and outcomes, we selected one effect measurement per study to include in the primary meta-analysis. The choice of the effect measurement was based on the following: (i) the shortest period of the exposure; for example, if a study reported 2 ORs/HRs—1 for antibiotics exposure within the first year of life and 1 for antibiotics exposure within the second year of life—the first year-estimated effect was included in the primary meta-analysis. Moreover, if ORs/HRs were reported for variable amounts of antibiotics (e.g, 1 course, 2 courses, 3 courses), the effect measurement of the largest sample size was included in the primary meta-analysis; (ii) the longest follow-up period for the outcome; for example, in a study that reported ORs/HRs for the association of early-life exposure to antibiotics and the occurrence of outcomes in children at the age of 4 years and children at the age of 8 years, the OR/HR associated with the outcome at 8 years was included in the primary meta-analysis.

Other reported ORs/HRs were used in subgroup meta-analyses.

2.5 | Data analysis

Overall pooled ORs, together with 95% confidence intervals (CIs) of the association between early-life exposure to antibiotics and allergies/atopies, were obtained using either a fixed-effects model or in case of heterogeneity, a random-effects model. Heterogeneity was identified using the I^2 statistic with a significance level of $\alpha = 0.05$, which quantifies inconsistency across studies included: 25% corresponding to low, 50% to moderate, and 75% to high heterogeneity. The primary meta-analyses included all studies on the association between exposure and outcomes and were run for hay fever, eczema, food allergy, positive SPT, and elevated serum/plasma IgE levels, separately.

Metaregression analyses were performed on the effect of the child's age at the time of antibiotics consumption and the age at the time of diagnosis.

To test the causal relation between antibiotics and outcomes, the second meta-analysis only included those studies that have explicitly reported that patients diagnosed with allergies/atopies are new incident cases at the time of outcome measurement.

In the third meta-analysis, the association between antibiotics and outcomes was studied by including only those studies that analyzed both allergic clinical symptoms (hay fever and eczema) and objective markers of allergy (we chose positive SPT as the most common allergy marker in individual studies) in the same patients.

Publication bias was evaluated using funnel plots where the Egger test was applied to measure any asymmetry. In this meta-analysis, for reasons of symmetry, the reported ORs and lower and upper bounds of the 95% CIs were initially log-transformed; the log ORs together with 95% CIs of the log ORs were meta-analyzed using either fixed- or random-effects models; then, the results were transformed back to the original ORs for reporting. *P*-values of <.05 were used to assess the statistical significance of main effect associations. All statistical analyses were conducted using STATA 10/SE (Stata Statistical Software: Release 10; StataCorp. 2007, College Station, TX, USA: StataCorp LP). For meta-analytic procedures, metan, metabias, and metareg commands were used.

[All sections related to data extraction, quality assessment, subgroup and sensitivity analyses as well as corresponding results, tables, and figures are presented as Supporting information].

3 | RESULTS

3.1 | Systematic search results

A flowchart (Figure 1) describes study identification, screening, and inclusion. Our literature search yielded 3839 published articles, and after applying the inclusion and exclusion criteria, a total of 34 studies [10-43] were selected for the meta-analysis.

3.2 | Study characteristics

The characteristics of the included studies are summarized in Table 1 for cohort studies (n = 20 studies), Table 2 for case-control studies (n = 6 studies), and Table 3 for cross-sectional studies (n = 8 studies); the design of these studies is based on what authors have stated in the manuscript. Twenty-two studies (including 229 080 patients) were selected to study the risk of hay fever, 22 studies (including 394 517 patients) to study the risk of eczema, 3 studies (including 23 878 children) to study the risk of food allergy, 10 studies (including 27 092 children) to study the risk of positive SPT, and 8 studies (including 16 043 children) to study the risk of elevated allergen-specific serum/plasma IgE levels. The studies assessing hay fever, eczema, and positive SPT as outcomes applied an exposure window of the first 2 years of life. The studies assessing food allergy and increased serum/plasma IgE levels applied a shorter exposure window, namely the first year of life. For the association between early-life antibiotics use and eczema, 2 studies were multicenter studies consisting of 193 412[20] and 6630[19] children. None of the studies that reported a positive significant association between antibiotics and hay fever or eczema had a positive significant association with atopies including positive SPT or elevated allergen-specific serum/plasma IgE levels.

3.3 | Antibiotics exposure and hay fever

Our primary meta-analysis showed a statistically significant higher risk of developing hay fever among children exposed to antibiotics during the first 2 years of life compared to never-exposed children in the same period of time, OR: 1.23 (95% CI: 1.13-1.34; I^2: 77.0%) (Figure 2).

3.4 | Antibiotics exposure and eczema

Children who were exposed to antibiotics in early life (first 2 years of life) had a statistically significantly increased risk of eczema later in life compared with those who were never exposed during the same time period, OR: 1.26 (95% CI: 1.15-1.37; I^2: 74.2%) (Figure 3).

3.5 | Antibiotics exposure and food allergy

Our meta-analysis showed a statistically significant relationship between early-life antibiotics consumption and the risk of food allergy later in life. The risk of food allergy was higher in children exposed to antibiotics during the first year of life compared with those in nonexposed group, OR: 1.42 (95% CI: 1.08-1.87; I^2: 80.8%) (Figure 4).

3.6 | Antibiotics exposure and positive skin prick test

Early-life antibiotics consumption (first 2 years) was not statistically significantly related to the risk of positive SPT later in life, OR: 1.01 (95% CI: 0.92-1.11; I^2: 54.8%) (Figure 5).

3.7 | Antibiotics exposure and elevated allergen-specific serum/plasma immunoglobulin E levels

The risk of elevated allergen-specific serum/plasma IgE levels later in life was not significantly associated with antibiotics consumption during the first year of life, OR: 0.95 (95% CI: 0.77-1.16; I^2: 44.9%) (Figure 6).

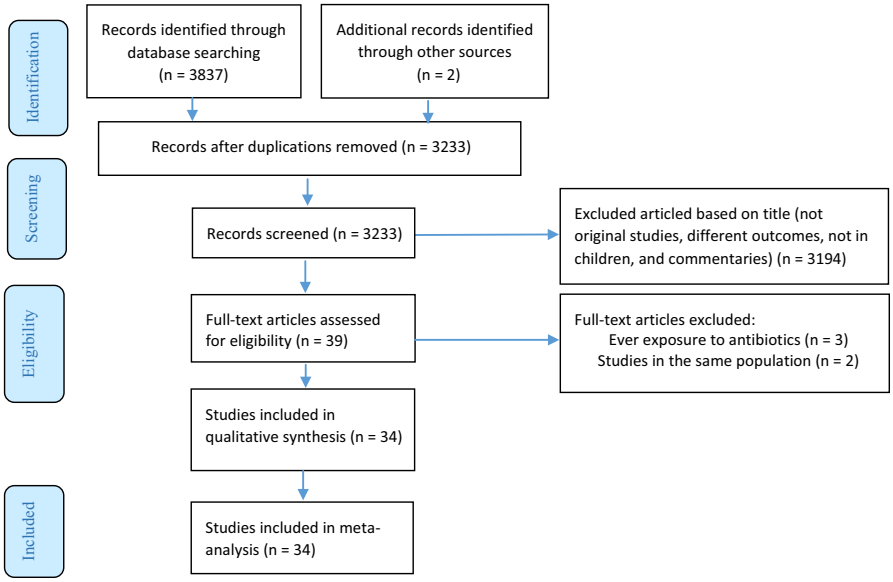

FIGURE 1 A flowchart diagram showing the progress of studies through the review

TABLE 1 Overview of cohort studies included in the meta-analysis

	Source	Country	Study goal	Study size	Antibiotics measurement	Subgroup of antibiotics assessment	Age at time of antibiotics use	Outcome (s) measurement	Age at time of allergy measurement	Extracted effect size (95% CI)
Prospective cohort										
1	Alm et al.[10]	Sweden	Antibiotics as a risk factor for allergic rhinitis	4051	Parental reported	-	First week	Parental reported of hay fever/physician diagnosis of allergic rhinitis	5.7 years (mean)	Allergic rhinitis OR: 1.75 (1.03-2.97)
2	Bohme et al.[11]	Sweden	Atopic dermatitis and concomitant disease patterns	4089	Parental reported	-	First 2 years	Parental reported of physician diagnosis of outcomes	12 months (mean)	Eczema calculated OR: 1.35 (1.17-1.57)
3	Celedón et al.[13]	US	Association of antibiotics and allergic rhinitis, or eczema, with a parental history of allergies	448	Parental reported	One course and ≥2 courses antibiotic	First year	Parental reported of outcomes	At the age of 5 years	Allergic rhinitis OR: 0.7 (0.3-1.5) Eczema OR: 1.1 (0.4-3.1)
4	Dom et al.[16]	the Netherlands	Postnatal exposure to antibiotics and the development of eczema/atopy	773	Parental reported	-	First year	Parental reported of physician diagnosis of outcomes—blood test	Up to 4 years	Eczema OR: 0.61 (0.36-1.01) Elevated IgE OR: 0.38 (0.21-0.71)
5	Harris et al.[21]	UK	Association between antibiotics and seasonal rhinitis/atopy	642	Prescription data	-	First year	Parental reported of outcomes based on ISAAC questionnaire—SPT	At the age of 8 years	Seasonal rhinitis OR: 1.08 (1.00-1.17) Positive SPT OR: 0.96 (0.87-1.07)
6	Hoskin-parr et al.[22]	UK	Association between antibiotics and asthma, eczema/hay fever/atopy	4952	Parental reported	≥2 courses antibiotic	First 2 years	Parental reported of physician diagnosis of outcomes—SPT	7.5 years (mean)	Eczema OR: 1.2 (1.02-1.41) Hay fever OR: 1.28 (1.03-1.6) Positive SPT OR: 1.00 (0.80-1.25)
7	Johnson et al.[23]	US	Association between antibiotics and atopy	725	Prescription data	Broad-spectrum antibiotic	First 6 months	Parental reported of outcomes—SPT—blood test	6-7 years (range)	Positive SPT OR: 1.48 (0.94-2.34) Elevated IgE OR: 1.16 (0.72-1.87)
8	Kummeling et al.[24]	the Netherlands	Association between antibiotics and eczema/atopy	2764	Parental reported	-	First 6 months	Parental reported of physician diagnosis of outcomes—blood test	First 2 years (range)	Eczema OR: 0.94 (0.75-1.18) Elevated IgE OR: 1.32 (0.86-2.02)

(Continues)

TABLE 1 (Continued)

	Source	Country	Study goal	Study size	Antibiotics measurement	Subgroup of antibiotics assessment	Age at time of antibiotics use	Outcome (s) measurement	Age at time of allergy measurement	Extracted effect size (95% CI)
9	Kusel et al.[25]	Australia	Association between antibiotics and eczema/atopy among high genetic risk of atopies	198	Daily diary for 5 years	-	First year	Physician diagnosis of outcomes—SPT—blood test	Up to 5 years	Eczema OR: 1.2 (0.6-2.5) Positive SPT OR: 0.6 (0.3-1.4) Elevated IgE OR: 1.00 (0.50-2.10)
10	Mai et al.[26]	Sweden	Association between antibiotics and eczema/hay fever/food allergy/atopy	3306	Parental reported	-	First year	Parental reported of physician diagnosis of outcomes—blood test	At the age of 4 and at the age of 8 years	Eczema OR: 1.3 (1.1-1.5) Allergic rhinitis OR: 1.1 (0.9-1.3) Food allergy OR: 1.4 (1.1-1.7) Elevated IgE OR: 0.9 (0.7-1.1)
11	McKeever et al.[27]	UK	Antibiotics and the incidence of eczema/hay fever	29 238	Prescription data	Types of antibiotic/1, 2, 3, and ≥4 courses antibiotic	First year	Physician diagnosis of outcomes	Eczema 2.2 years Hay fever 3.5 years (mean)	Eczema HR: 1.22 (1.12-1.34) Hay fever HR: 1.14 (0.94-1.38)
12	Ponsonby et al.[32]	Australia	Association between antibiotics and hay fever	863	Parental reported	-	First month	Parental reported of outcomes based on ISAAC questionnaire	2.1 years (mean)	Hay fever: calculated OR: 1.14 (0.70-1.85)
13	Risnes et al.[35]	US	Association between antibiotics and asthma/atopy	1401	Parental reported	Frequency of antibiotic: once, twice, ≥3 times/one and ≥2 courses antibiotic	First 6 months	SPT	At the age of 6 years	Positive SPT OR: 1.59 (1.10-2.28)
14	Sandini et al.[36]	Finland	Protective and risk factors for allergic diseases in high-risk children	1223	Parental reported	-	First 6 months	Physician diagnosis of outcomes—blood test	At the age of 2 years and at the age of 5 years	Eczema OR: 1.20 (0.79-1.81) Allergic rhinitis OR: 0.92 (0.54-1.56) Elevated IgE OR: 0.82 (0.54-1.25)
15	Schmitt et al.[37]	Germany	Association between antibiotics and eczema	370	Health insurance database	Type of antibiotic	First year	Health insurance database, which is based on physician diagnosis of outcomes	1-2 years (range)	Eczema calculated OR: 1.52 (0.73-3.14)

(Continues)

TABLE 1 (Continued)

	Source	Country	Study goal	Study size	Antibiotics measurement	Subgroup of antibiotics assessment	Age at time of antibiotics use	Outcome (s) measurement	Age at time of allergy measurement	Extracted effect size (95% CI)
16	Sobko et al.[38]	Sweden	Association between antibiotics and eczema/hay fever	Cases: 203 controls: 426	Prescription data	-	At birth time	Parental reported of outcomes based on ISAAC questionnaire	12 years (median)	Eczema OR: 0.94 (0.66-1.36) Hay fever OR: 1.28 (0.75-2.17)
17	Su et al.[42]	US	Association between antibiotics and asthma/ eczema/atopy	424	Parental reported	-	First 9 months	Parental reported of outcome—blood test	1-5 years (range)	Eczema calculated OR: 1.04 (0.52-2.1) Elevated IgE calculated OR: 1.13 (0.63-2.03)
18	Wickens et al.[43]	New Zealand	Association between antibiotics and eczema	1,105	Parental reported	-	First 3 months	Parental reported of outcomes based on ISAAC questionnaire—SPT	At 15 months and 4 years	Eczema OR: 1.52 (0.87-2.65) Positive SPT OR: 1.49 (1.03-2.15)
Retrospective cohort										
19	Cullinan et al.[15]	UK	Association between antibiotics and hay fever/atopy	746	Prescription data	Type of antibiotic	First year	Parental reported of physician diagnosis of hay fever—SPT	19-46 years (range)	Hay fever OR: 0.95 (0.80-1.13) Positive SPT OR: 0.86 (0.73-1.02)
20	Farooqi et al.[18]	UK	Early childhood antibiotics consumption and eczema/hay fever	1,934	Prescription data	Type of antibiotic/1, 2, and 3 courses antibiotic	First 2 years	Physician diagnosis of outcomes	6-12	Eczema OR: 2.04 (1.53-2.73) Hay fever OR: 2.04 (1.59-2.62)

CI, confidence interval; OR, odds ratio; HR, hazard ratio; SPT, skin prick test; IgE, immunoglobulin E.

TABLE 2 Overview of case-control studies included in the meta-analysis

	Source	Country	Study goal	Study size	Antibiotics measurement	Subgroup of antibiotics assessment	Age at time of antibiotics measurement	Outcome(s) measurement	Age at time of allergy measurement	Extracted effect size (95% CI)
1	Bremner et al.[12]	UK	Association between antibiotics and hay fever	Cases: 7,098 controls: 7098	Prescription data	Broad-spectrum antibiotic/1-2 and ≥3 courses antibiotic/type of antibiotic/duration of antibiotic	First year	Physician diagnosis of outcomes	GPRD: 4.6 years (mean) DIN: 5.1 years (mean)	Hay fever OR GPRD: 1.08 (0.98-1.2) DIN: 1.15 (1.03-1.29)
2	Cohet et al.[14]	New Zealand	Antibiotics and the prevalence of symptoms of eczema/rhinitis	Cases: 1584 controls: 2539	Parental reported	-	First year	Parental reported of outcomes based on ISAAC questionnaire	6-7 years (range)	Eczema OR: 1.40 (1.21-1.62) Hay fever OR: 1.52 (1.25-1.85)
3	Metsala et al.[28]	Finland	Association between antibiotics and food allergy	Cases: 16 237 controls: 16 237	Prescription data	Type of antibiotic	First month	Physician diagnosis of outcome	1 month to 8 years (range)	Cow's milk allergy OR: 1.71 (1.59-1.84)
4	Mullooly et al.[30]	US	Association between antibiotics and atopic eczema/hay fever	Cases: 844 controls: 230	Dispensing data	-	First 2 years	Parental reported of outcomes—SPT	10.3 years (mean)	Eczema OR: 1.02 (0.96-1.10) Allergic rhinitis OR: 1.03 (0.97-1.08) Positive SPT OR: 0.95 (0.89-1.01)
5	Purvis et al.[33]	New Zealand	Risk factors for atopic dermatitis	Cases: 87 controls: 463	Parental reported	-	First year	Dermatitis by trained investigator	3.5-4 years (range)	Eczema OR: 1.18 (0.61-2.26)
6	Thomsen et al.[41,a]	Denmark	Early-life exposures and hay fever	480	Parental reported	-	First 2 years	Parental reported of outcomes	12.1 years (mean)	Hay fever OR: 0.73 (0.38-1.40)

CI, confidence interval; OR, odds ratio; SPT, skin prick test.
[a]Case cohort study.

TABLE 3 Overview of cross-sectional studies included in the meta-analysis

	Source	Country	Study goal	Study size	Antibiotics measurement	Subgroup of antibiotics assessment	Age at time of antibiotics measurement	Outcome(s) measurement	Age at time of allergy measurement	Extracted effect size (95% CI)
1	Droste et al.[17]	Belgium	Association between antibiotics and eczema/hay fever/atopy—high-risk children	1206	Parental reported	-	First year	Parental reported of outcomes—SPT	7-8 years (range)	Eczema OR: 1.3 (1.00-1.80) Hay fever OR: 2.3 (1.3-3.8) Positive SPT OR: 1.1 (0.7-1.7)
2	Muc et al.[29]	Portugal	Association between antibiotics and rhinitis	1063	Parental reported	-	First year	Parental reported of outcomes based on ISAAC questionnaire	7.2 years (mean)	Rhinitis OR: 1.81 (1.26-2.60)
3	Mutius et al.[31]	Germany	Association between antibiotics and eczema/hay fever/atopy	15 043	Parental reported	1-2, 3-5, and ≥courses antibiotics	First 2 years	Parental reported of physician diagnosis of outcomes based on ISAAC questionnaire—SPT	5-11 years (range)	Eczema OR: 1.26 (1.05-1.52) Hay fever OR: 1.12 (0.84-1.50) Positive SPT OR: 0.96 (0.80-1.17)
4	Raciborski et al.[34]	Poland	Association between antibiotics and eczema/hay fever/ food allergy	1330	Parental reported	Frequency of antibiotics: once, 1-2 times, 2-3 times, 3-4 times, and >4 times	First year	Parental reported of outcomes based on ISAAC questionnaire	6-8 years (range)	Eczema OR: 1.43 (1.08-1.91) Hay fever OR: 1.28 (0.88-1.85) Food allergy OR: 1.30 (0.89-1.89)
5	Sultész et al.[39]	Hungary	Prevalence and risk factors for allergic rhinitis	6335	Parental reported	-	First year	Parental reported of physician diagnosis of outcomes	6-12 years (range)	Allergic rhinitis OR: 1.60 (1.37-1.87)
6	Tamay et al.[40]	Turkey	Prevalence and risk factors for allergic rhinitis	2500	Parental reported	-	First year	Parental reported of physician diagnosis of outcomes based on ISAAC questionnaire	6-12 years (range)	Allergic rhinitis OR: 1.26 (1.01-1.57)

(Continues)

TABLE 3 (Continued)

	Source	Country	Study goal	Study size	Antibiotics measurement	Subgroup of antibiotics assessment	Age at time of antibiotics measurement	Outcome(s) measurement	Age at time of allergy measurement	Extracted effect size (95% CI)
Multicenter studies										
7	Foliaki et al.[20]	71 centers in 29 countries	Association between antibiotics and eczema	193 412	Parental reported	-	First year	Parental reported of outcomes	6-7 years (range)	Eczema OR: 1.42 (1.33-1.51)
8	Floistrup et al.[19]	the Netherlands, Austria, Germany, Sweden, Switzerland	Antibiotics use and eczema/atopy (pooled results)	6630	Parental reported	-	First year	Parental reported of physician diagnosis of outcomes—blood test	9.1 years (mean)	Eczema OR: 1.63 (1.22-2.17) Elevated IgE OR: 0.91 (0.60-1.37)

In cross-sectional studies, both exposure and outcome were questioned at one point of time; however, the period over which exposure and outcome were requested was different, and therefore, these studies have been accepted in our meta-analyses.
CI, confidence interval; OR, odds ratio; SPT, skin prick test; IgE, immunoglobulin E; SPT, skin prick test.

3.8 | Causal inference

To evaluate the causality and avoid confounding by reverse causation, a second meta-analysis was run by including only those studies that explicitly reported that the exposure to antibiotics preceded the occurrence of hay fever (6 studies including 184 257 patients)[10,12,18,21,27,38] and eczema (8 studies including 156 924 patient).[16,18,25-27,37,38,43] The results showed that early-life antibiotics consumption (first 2 years) was statistically significantly related to the risk of hay fever (OR: 1.23; 95% CI: 1.08-1.41; I^2: 77.3%) and the risk of eczema (OR: 1.25; 95% CI: 1.03-1.52; I^2: 68.2%) later in life.

Our results in the third meta-analysis showed a nonsignificant increased risk of hay fever (OR: 1.13; 95% CI: 0.97-1.32; I^2: 69.9%) and positive SPT (OR: 0.95; 95% CI: 0.90-1.00; I^2: 0.0%) in 5 studies that both assessed clinical and objective marker of hay fever (n = 23 021 patients in total). However, the association between antibiotics and risk of eczema and SPT showed a statistically significant result for eczema (OR: 1.17; 95% CI: 1.03-1.32; I^2: 48.3%), but not for positive SPT (OR: 0.99; 95% CI: 0.89-1.11; I^2: 33.2%) in 6 studies that both reported clinical and objective marker of eczema (n = 23 578 patients in total).

3.9 | Publication bias

As shown in Fig. S1, there was no evidence of asymmetry to show potential publication bias in the primary meta-analyses for eczema (P = .52), food allergy (P = .43), positive SPT (P = .14), and elevated allergen-specific serum/plasma IgE levels (P = .38). Asymmetry appeared in the funnel plot for the association between antibiotics and hay fever (P = .01). This means that small studies showing a strong association probably have not been published yet.

3.10 | Metaregression

We conducted a metaregression analysis to identify the independent effect of variables (child's age at the time of antibiotics consumption and patient's age at the time of diagnosis of allergies/atopies) on the ORs. The age at which elevated allergen-specific IgE levels were observed, was found as the only predictor of the estimated OR (P-value: .05). However, we tested whether any clinical manifestations of allergies including eczema or eczema and hay fever together had more weight on the results. Our results showed that none of the clinical manifestation of allergies including eczema (P = .83) or eczema and hay fever together (P = .81) affected the predictive effect of age on specific IgE serum/plasma level (Table S2).

4 | DISCUSSION

To the best of our knowledge, this systematic review and meta-analysis provides the first large quantitative summary estimate of the association between early-life exposure to antibiotics and the risk of

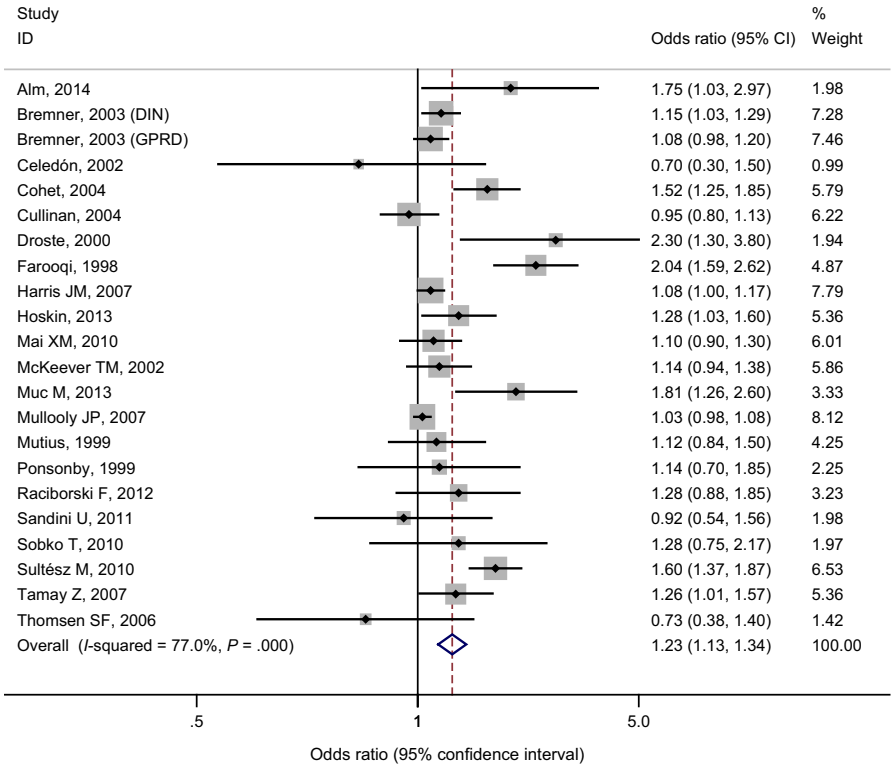

FIGURE 2 Association between early-life exposure to antibiotics and risk of hay fever later in life

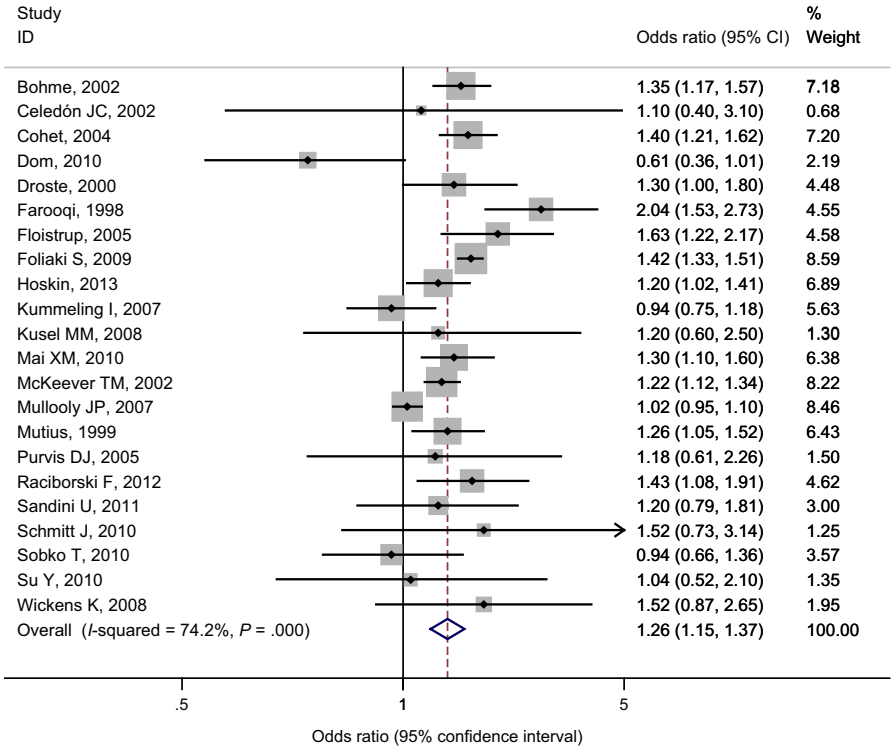

FIGURE 3 Association between early-life exposure to antibiotics and risk of eczema later in life

developing allergy and atopy later in life. Our main meta-analysis (including 34 studies and 340 428 patients) showed that exposure to antibiotics during the first 2 years of life is associated with an increased risk of hay fever, eczema, and food allergy later in life. However, remarkably, there was no association between exposure to antibiotics early in life and a positive SPT or elevated allergen-specific serum/plasma IgE levels later in life.

It remains unclear which mechanism may underlie the observed increased risk of hay fever, eczema, and food allergy among children exposed to antibiotics in early childhood. One hypothesis is that

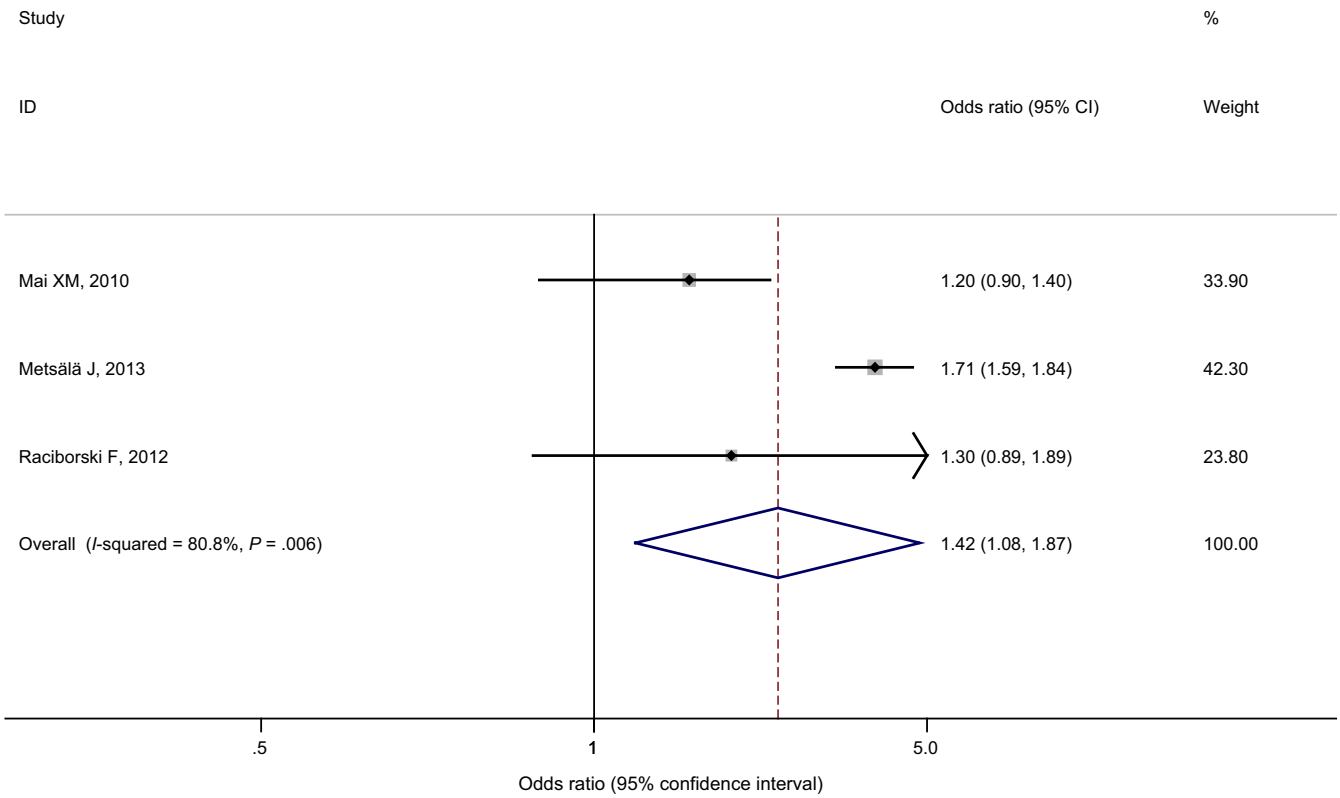

FIGURE 4 Association between early-life exposure to antibiotics and risk of food allergy later in life

antibiotics have immunomodulatory effects through their action on the gut microbiota, which may influence the risk of allergic disorders.[48,49] However, our positive results might also be explained by confounding by indication; individuals more prone to develop allergic diseases later in life might have been more prone for other conditions due to immunological incompetence requiring antibiotics use early in life.[50]

In our study, antibiotic exposure was associated with an increased risk of clinical allergic manifestations, but to our surprise, not with an increased risk of allergic sensitization. This was still true when we studied these outcomes in the same patients, even though the association with hay fever was no longer statistically significant in this smaller group. However, it should be noted that there is no clear relationship between allergic sensitization and allergic symptoms.[17,51-53] Although allergic sensitization often overlaps with the occurrence of allergic symptoms, there are also many children without allergen-specific serum IgE/positive SPT that do develop allergic symptoms [17,19,21,22,26,31] and vice versa.[43] There might be a different mechanism for allergic symptoms and atopy mediated through early-life antibiotics use. Children with a different genetic constitution or with a different history of exposure to protective factors such as breastfeeding might have different susceptibility to the effects of antibiotics. These children might also differ in their allergen-specific IgE levels. Previous studies have rigorously discussed how IgE sensitization translates into clinical allergy and that many different factors, for example, family history of atopy, have been associated with the clinical presentation of allergic symptoms in children with a positive (specific) serum IgE test.[54-56]

More solid evidence for the association between antibiotics exposure and clinical manifestations of allergies would require a randomized control study, which is not feasible to perform in this setting due to ethical reasons.

There are several potential limitations in the current study that should be addressed. Firstly, study design, the methods to analyze the data, and confounders involved in the adjusted models are not consistent across the studies included. Cross-sectional studies are limited by the fact that they are carried out at one point in time to obtain information on all factors (exposure, outcome, and confounders). Therefore, no conclusions about causal relationships can be drawn from studies with this design. However, in the self-defined cross-sectional studies that we have included in our meta-analysis (Table 3), the exposure to antibiotics was requested from a period in the past. Immunodeficiencies of childhood are a common cause for both infections and allergic disorders; these are potential confounders that have not been taken into account in studies included in the meta-analysis. There was a high degree of heterogeneity in patient's characteristics, for example, child's age at the time of antibiotics consumption and patient's age at the time of outcome measurement. These heterogeneities might have contributed to the discrepant results reported by previous epidemiological studies. However, our results were robust and consistent across the different subset of studies, for example, distinct study designs and different patient's characteristics. In pediatric allergic or atopic-related disorders, the timing of antibiotics consumption might be of importance, in which the first 6 months of life has been suggested to be the

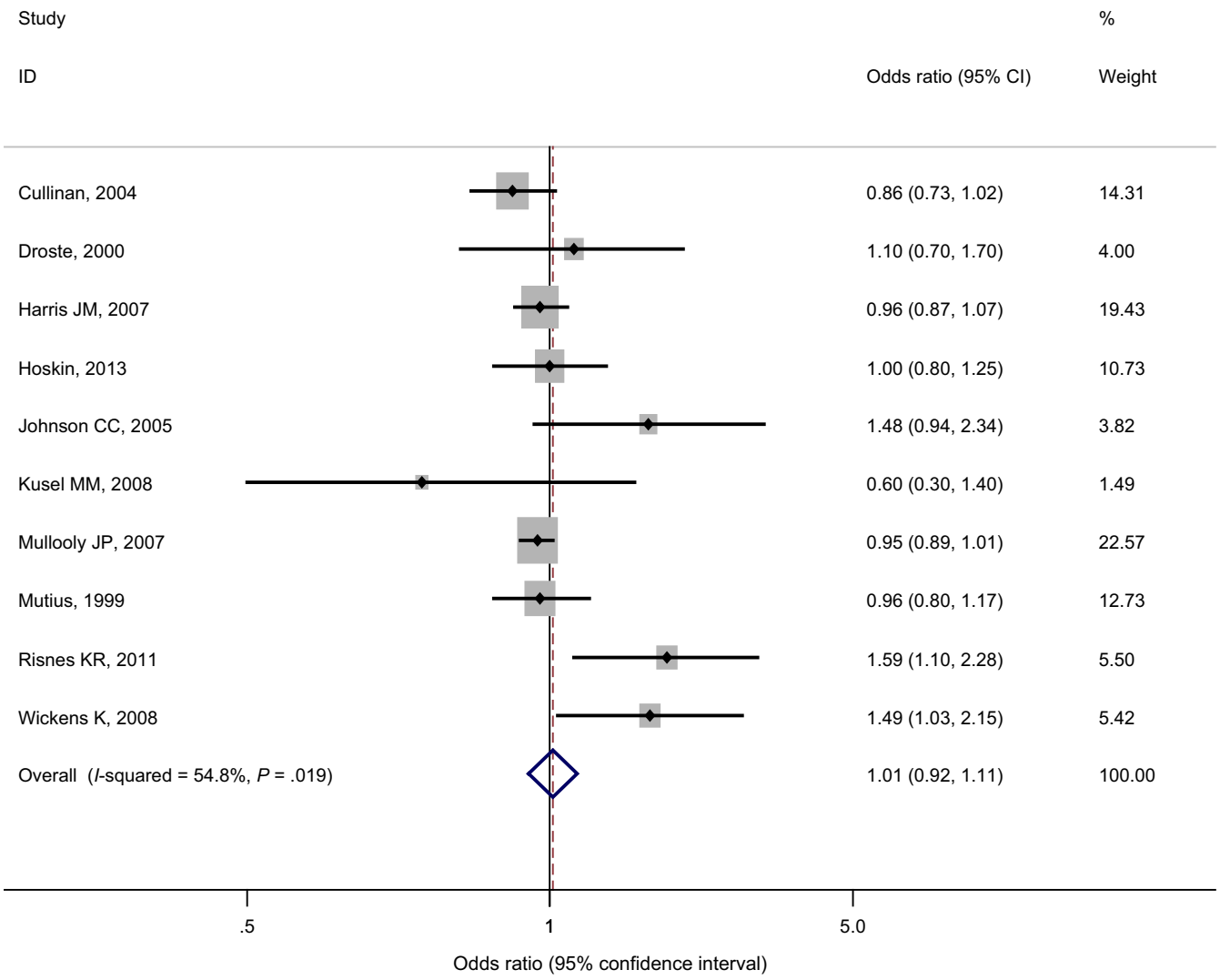

FIGURE 5 Association between early-life exposure to antibiotics and risk of positive skin prick test later in life

critical period.[57] The association of exposure to antibiotics in 3-week-old mice with increased risk of atopies measured by IgE serum levels has been already shown.[58] In addition, Wickens et al. have shown the significantly increased risk of positive SPT in children exposed to antibiotics during the first 3 months.[43] Although in our meta-analysis we were limited to test this association in the first 3 months (low number of studies included), we found very similar results for this association in the first 6 months of exposure to antibiotics (data not shown).

As presented in Figure 2, there is heterogeneity in the results of association between antibiotics and hay fever in the primary studies in which the association is not statistically significant in 12 studies included in our meta-analysis. However, the point estimates in 67% of these studies (8 of 12 studies) are above 1 and the 95% confidence intervals of all these 23 studies largely overlapped. Some of these individual studies may have been underpowered to identify a significant association due to small sample size. Furthermore, the differences in outcome definitions and more importantly differences in the ages of the children at the time of hay fever diagnosis in these studies might also explain the observed heterogeneity. Finally, one cannot rule out a possibility of imprecise diagnosis, in particular, of hay fever symptoms.

Dealing with heterogeneity was limited in the association between antibiotics and risk of food allergy. Studies selected for this association were extremely heterogeneous, most importantly, in the definition of the outcome. Food allergy is phenotypically a very wide-ranging group of diseases, which is often confused with other disorders, for example, celiac disease.[59] To confirm the significant positive association reported by our study, further research is needed.

Another important limitation consists of poor reporting of the types and the amount of antibiotics courses taken; this was often not mentioned in the studies. Previous studies reported that early use of broad-spectrum antibiotics was more strongly related to an altered gut microbiome and therefore the increased risk of allergies compared with narrow-spectrum antibiotics.[12,15,18,23,27,28,37] Unfortunately, we could not study the difference between broad- and narrow-spectrum antibiotics because the number of studies that

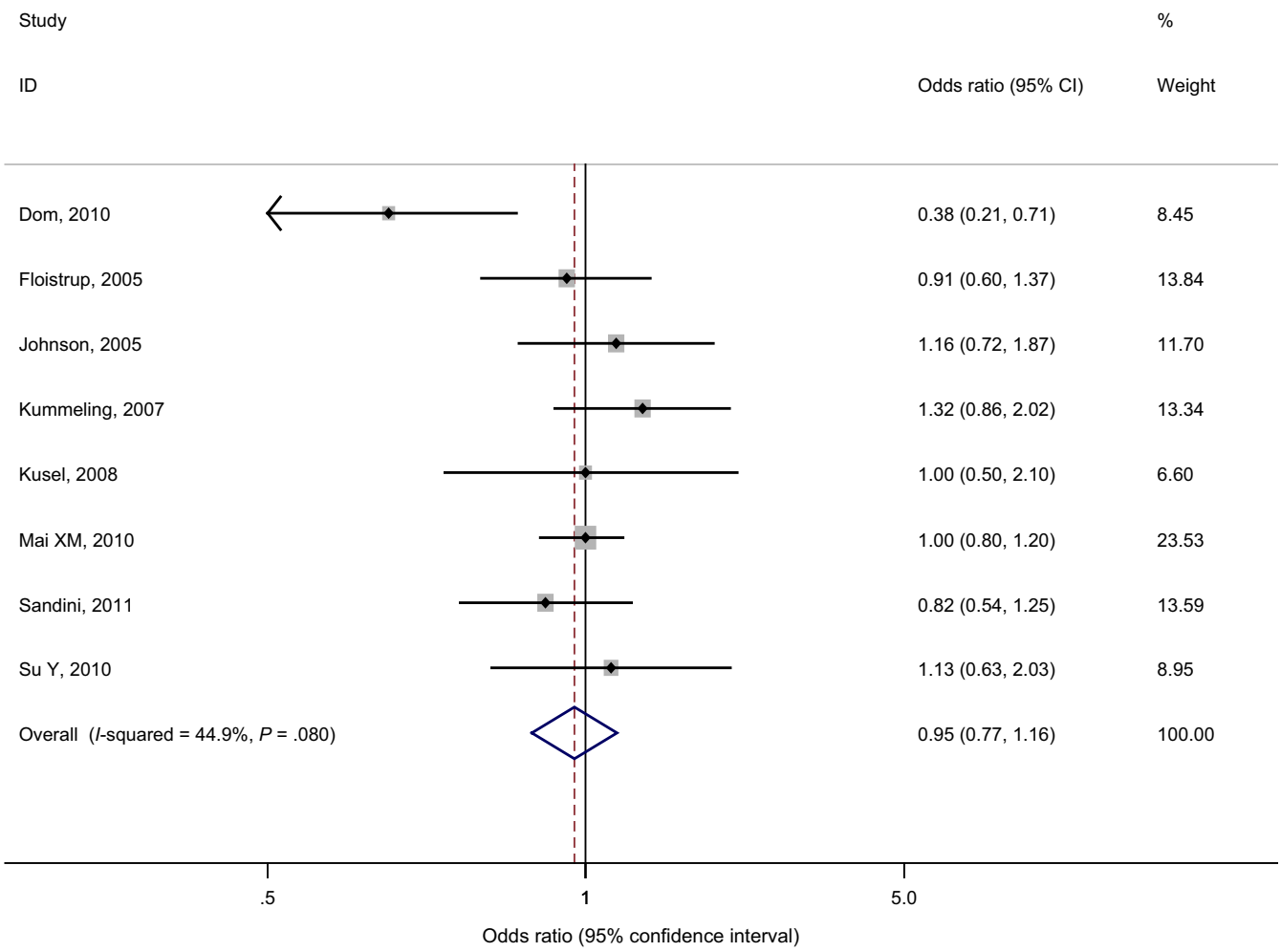

FIGURE 6 Association between early-life exposure to antibiotics and risk of elevated serum/plasma immunoglobulin E level later in life

reported the association stratified by type of antibiotics was not sufficient. The present study was also limited by including studies that used the parental-reported exposure to antibiotics (n = 23), which might be prone to recall bias. Parents may not always be able to remember and give accurate information on their child's medication use especially when the time of exposure is long ago. However, the results of our subgroup meta-analyses, separately for each outcome, showed no significant difference between the pooled effect estimates in studies with parental-reported measurement of antibiotics compared with medical/pharmacy record-based studies.

Moreover, hay fever, eczema, and food allergy were based on subjective symptoms and not objectively measured in a number of studies (n = 25); therefore, there is a risk of misclassification. For instance, the definition of hay fever/allergic rhinitis was not based on skin testing and/or evaluation of specific IgE; this might result in a misclassification of this outcome especially in children younger than 5 years who are prone to upper respiratory tract infections. Nevertheless, results of our study were similar to studies that used questionnaire-based outcomes compared with studies that used medical record-based outcomes.

In sensitivity analyses, we could only include parental allergy which is known to have a large impact on the association between antibiotics and allergy.[36] Although various variables may impact the risk of developing allergic disorders, not all these variables were available in the distinct studies.

The putative association between antibiotics and allergies could be caused by reverse causation in which children were prescribed antibiotics to treat symptoms related to allergies. Only 11 of 34 studies included explicitly reported that the use of antibiotics preceded the diagnosis of allergies.[10,12,16,18,21,25-27,37,38,43] In our meta-analysis, we tested the association between antibiotics and risk of hay fever and eczema only in these 11 studies to infer causality and the results still showed a significant association.

We tested the robustness of our findings using multiple subgroup and sensitivity analyses and consistently found an association between antibiotics exposure early in life and hay fever, eczema, and food allergy later in life. However, it remains unclear what causes this association. Further research into the impact of antibiotics on gut microbiome and related immune fitness is warranted. As inappropriate use of antibiotics in children is a major public health issue,[60] we strongly suggest more attention to improve healthcare quality by defining prognostic and diagnostic markers and recognizing children who never benefited from antibiotics therapy,

for example, those with the diagnosis of influenza.[61] Additionally, it is important to focus on educational programs in both individual patients and clinicians regarding judicious use of antibiotics.[62] Intervention studies including both patient and clinician awareness have shown that the inappropriate use of antibiotics was significantly reduced, for instance, by displaying poster-sized commitment letters in examination room.[60]

The appropriate use of probiotics has been shown as a plausible factor to affect the gut microbiome composition in children treated with antibiotics.[63] Since 2005, clinical guidelines such as "Probiotics for the Prevention of Antibiotic-Associated Diarrhea in Children" promote the use of probiotics when antibiotics are prescribed in children. Twenty-three of the studies included in our study are from 2005 or later, and in these studies, probiotics use might have occurred. Nevertheless, this was not reported. Overall, appropriate use of probiotics during and after an antibiotic course could have attenuated the negative effect of antibiotics on the gut microbiota.

CONFLICTS OF INTEREST

The authors have no conflicts of interest relevant to this article to disclose.

AUTHOR CONTRIBUTONS

Fariba Ahmadizar: Dr. Ahmadizar is responsible for the study concept and design, analyzing the accuracy of the data, the interpretation of data, and writing the manuscript and approved the final manuscript as submitted. Susanne J. H. Vijverberg: Dr. Vijverberg is responsible for study concept and design, the interpretation of data, and revising the manuscript and approved the final manuscript as submitted. Hubertus G. M. Arets: Dr. Arets critically reviewed and revised the article and approved the final manuscript as submitted. Anthonius de Boer: Prof. Dr. de Boer is responsible for study concept and design, the interpretation of data, and revising the manuscript and approved the final manuscript as submitted. Jason E. Lang: Dr. Lang critically reviewed and revised the article and approved the final manuscript as submitted. Johan Garssen: Prof. Dr. Garssen critically reviewed and revised the article and approved the final manuscript as submitted. Aletta D. Kraneveld: Prof. Dr. Kraneveld critically reviewed and revised the article and approved the final manuscript as submitted. Anke H. Maitland-van der Zee: Prof. Dr. Maitland-van der Zee is responsible for study concept and design, the interpretation of data, and revising the manuscript and approved the final manuscript as submitted. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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