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Prenatal or Early-Life Exposure to Antibiotics and Risk of Childhood Asthma: A Systematic Review

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KEY WORDS

antibiotics, asthma, meta-analysis, systematic review

ABBREVIATIONS

CI—confidence interval

OR—odds ratio

RR—relative risk

HR—hazard ratio

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abstract

CONTEXT: The increasing prevalence of childhood asthma has been associated with low microbial exposure as described by the hygiene hypothesis.

OBJECTIVE: We sought to evaluate the evidence of association between antibiotic exposure during pregnancy or in the first year of life and risk of childhood asthma.

METHODS: PubMed was systematically searched for studies published between 1950 and July 1, 2010. Those that assessed associations between antibiotic exposure during pregnancy or in the first year of life and asthma at ages 0 to 18 years (for pregnancy exposures) or ages 3 to 18 years (for first-year-of-life exposures) were included. Validity was assessed according to study design, age at asthma diagnosis, adjustment for respiratory infections, and consultation rates.

RESULTS: For exposure in the first year of life, the pooled odds ratio (OR) for all studies ($N = 20$) was 1.52 (95% confidence interval [CI]: 1.30–1.77). Retrospective studies had the highest pooled risk estimate for asthma (OR: 2.04 [95% CI: 1.83–2.27]; $n = 8$) compared with database and prospective studies (OR: 1.25 [95% CI: 1.08–1.45]; $n = 12$). Risk estimates for studies that adjusted for respiratory infections (pooled OR: 1.16 [95% CI: 1.08–1.25]; $n = 5$) or later asthma onset (pooled OR for asthma at or after 2 years: OR: 1.16 [95% CI: 1.06–1.25]; $n = 3$) were weaker but remained significant. For exposure during pregnancy ($n = 3$ studies), the pooled OR was 1.24 (95% CI: 1.02–1.50).

CONCLUSIONS: Antibiotics seem to slightly increase the risk of childhood asthma. Reverse causality and protopathic bias seem to be possible confounders for this relationship. *Pediatrics* 2011;127:1125–1138

Asthma, which has an estimated 10% worldwide prevalence among children aged 6 to 7 years, is one of the most common chronic childhood diseases.¹ Observations that developed countries show higher prevalences of asthma than developing countries¹ have led to the “hygiene hypothesis,” which postulates that childhood development in an overly hygienic environment reduces microbial exposure and promotes atopic immune responses and the risk of asthma.² Results of experiments in mice have supported this hypothesis, demonstrating that bacterial gut colonization in early life plays a significant role in acquired immune system programming.^{3–6} In utero microbial exposures have also been shown to protect against allergic phenotypes in mice.^{7–9} Perturbation to normal microbial exposure during gestation or infancy, therefore, may elevate the risk of atopic disease including asthma. In consideration of this hypothesis, numerous studies to date have attempted to evaluate the association between antenatal and infant antibiotic usage and subsequent development of asthma.

This research is highly susceptible to several possible biases that confound the true association between antibiotics and asthma.¹⁰ Reverse causality, which occurs when the outcome precedes and increases the risk for the putative exposure, may be a strong source of bias for studies that fail to accurately determine the relative timing of antibiotic use and the onset of asthma. This is a particular concern because patients with asthma may receive antibiotics at elevated rates, either by misprescription or for treatment of comorbidities.¹¹ Studies that assess outcomes of ever or current, but not incident (ie, onset), asthma may be susceptible to reverse causality even if measured after the time of exposure. A specific type of reverse

causality is protopathic bias, which occurs when early symptoms of undiagnosed asthma are attributed mistakenly to respiratory infection and are treated with antibiotics. Diagnosis of asthma in children may occur up to several years after the onset of respiratory symptoms,^{12,13} which suggests that studies that use a short “wash-out” period between antibiotic exposure and outcome assessment may be susceptible to protopathic bias. Detection bias, which occurs when the likelihood of diagnosis is influenced by the patient’s frequency of physician consultations, may also be an issue.¹² Indication bias, which occurs when respiratory infections are treated with antibiotics while being independent risk factors for asthma, is likewise a strong possibility.^{14–16} Finally, recall bias may be a confounder for retrospective studies, because parents of children with asthma may be more likely to recall early life exposures.

The purpose of this review was to systematically evaluate evidence from studies that addressed 2 questions: “Does antibiotic exposure in the first year of life increase the risk of asthma in children aged 3 to 18 years?” and “Does antibiotic exposure during pregnancy increase the risk of asthma in offspring by the age of 18 years?” For the first question, the separation of at least 2 years between exposure and outcome was chosen to reduce the likelihood of reverse causality or protopathic bias in the included studies.

A previous systematic review in 2006 by Marra et al¹⁷ similarly examined the evidence for association between antibiotic exposure in the first year of life and childhood asthma, but the results of numerous studies that addressed this question have been published since then.

Evidence of a true association between antibiotic use and childhood asthma would further support the

reduction of unnecessary antibiotic prescriptions during pregnancy and in early life and add support for the hygiene hypothesis.

METHODS

A completed PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) 2009 checklist for this systematic review is available in [Supplemental Table 3](#). A protocol for this review has not been previously published.

Search Strategy and Study-Selection Criteria

PubMed was searched between the date of index start (1950) and July 1, 2010. The search was not restricted by language. The following query string was used: (child or childhood or “early life” or “early child” or postnatal or pediatric or prenatal or antenatal or pregnancy or “in utero” or maternal or infant or mothers or mother or “maternal exposure” or “maternal exposures” or “prenatal exposure delayed effects” or “prenatal care”) and (asthma* or wheezing or atopy or COPD or “chronic obstructive pulmonary disease” or bronchitis or bronchiolitis) and (antibiotic* or antimicrobial or antibacterial or “anti-bacterial agents”).

A publication was selected for further evaluation if it met inclusion criterion of evaluating an association between exposure to antibiotics and an outcome of childhood asthma. Outcomes defined as “wheeze” or “wheezing” but not asthma were not included. A study was excluded from final analysis if it met 1 of the following criteria: (1) there was no reported age of exposure or outcome; (2) only mixed exposures or outcomes were assessed (ie, exposure to antibiotics and another factor or development of asthma and another condition); (3) antibiotic exposure was assessed after 1 year of age only; (4)

asthma was assessed before 3 years only (for studies of childhood exposure); (5) outcomes were assessed after 18 years of age only; or (6) there was a lack of a reported statistical measure of association or enough data to allow for its calculation. If a study assessed asthma that could have been diagnosed before 3 years but also included any of years 3 to 18 in its follow-up, it was still included in this study. Each included study was scored on the basis of a modified Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist,¹⁸ and studies were excluded if they had <50% of STROBE checklist criteria.

Data Extraction

Studies were evaluated and abstracted by 2 independent reviewers (Mr Murk and Dr Risnes); discordant data abstraction was resolved by consensus and discussion with a third reviewer (Dr Bracken). For each included study, data were collected regarding study design, population size in each study group, criteria for eligibility, time of antibiotic use, type of antibiotic used, number of prescriptions for antibiotics, reasons for antibiotic use, method of determining antibiotic exposure, time of asthma diagnosis, method of determining asthma diagnosis, risk estimates with 95% confidence intervals (CIs), respiratory infections between ages 0 and 1 year, number of medical consultations (visits to a physician) between ages 0 and 1 year, family history of asthma, and other covariates used to adjust the risk estimates. If the authors of a study reported multiple comparisons of antibiotic and exposure, the comparison that was judged to be the least biased (eg, had an older first possible age of asthma diagnosis or was adjusted for respiratory infections or other factors mentioned above) was included for the final analysis. When the authors re-

ported an adjusted estimate for the whole cohort, as well as for a subgroup with asthma first diagnosed at or after 2 years of life, the overall results were included in the appropriate main analysis, and the latter was included in comparisons of age of diagnosis-related subgroups.

Retrospective studies were defined as those studies that assessed exposures by self-report after they had already occurred. Database studies were assessed as a separate type of study design and were defined as those that assessed exposures via a medical practice or administrative database.

Statistical Methods

The effect measure used in the meta-analysis was the adjusted odds ratio (OR), relative risk (RR), or hazard ratio (HR) for asthma. If no adjusted effect measure was provided, then the crude measure was used. Meta-analysis was performed by using random-effects and fixed-effects models; the fixed-effects models were only used when low or moderate heterogeneity was detected. When not otherwise specified, pooled estimates mentioned in the text are from a random-effects model. Effect measures were weighted by log inverse variance. Heterogeneity was assessed by using Cochran's Q (χ^2) statistic ($P < .10$ was considered significant evidence for heterogeneity), the I^2 test (values of >40% and >75% were considered to indicate moderate and high heterogeneity, respectively), and visual inspection of Galbraith plots. Sources of heterogeneity were investigated by performing subgroup sensitivity analyses of studies on the basis of the following prespecified factors: study design (retrospective, database, or prospective study design); age of asthma onset (0–1 vs ≥ 2 years); asthma definition (doctor-diagnosed versus parental report of “having asthma”); use of an

RR/HR or an OR effect estimate; adjustment for respiratory infections; adjustment for number of medical consultations; and adjustment for family history of asthma. Comparison of pooled effect estimates was performed by using a test of interaction for normally distributed differences in effect estimates.¹⁹ Publication bias was evaluated by visual inspection of funnel plots and by using Egger's asymmetric distribution test; $P < .10$ was considered significant.²⁰

Statistical significance for pooled estimates was defined by using $\alpha = .05$. Calculations were performed by using Review Manager (RevMan) 5.0 (Cochrane Collaboration, Oxford, United Kingdom [www.cc-ims.net/revman]) and SAS 9.0 (SAS Institute Inc, Cary, NC).

RESULTS

Study Selection

The literature search identified 2071 citations, of which 29 assessed the association between antibiotics and asthma (Fig 1). Of these 29 studies, 7^{21–27} were excluded because they met exclusion criterion (see [Supplemental Table 4](#)): 3 studies only examined antibiotic exposures after 1 year of age, and 4 studies only examined mixed outcomes (asthma with another morbidity). The remaining 22 studies were included in the final analysis. Characteristics of the included studies that assessed exposure in infancy^{28–47} ($n = 20$) are listed in Table 1, and studies of in utero exposures^{40,48,49} ($n = 3$) are listed in Table 2. Two of the included studies met strict exclusion criteria by exceeding age of exposure (Wickens et al⁴⁵; exposure age: 0–15 months) or outcome (Sobko et al⁴³; asthma outcome age: 7–23 years [median age: 7]) limits, but they were retained because it was judged that these ages of exposure/outcome were not substantially different from those

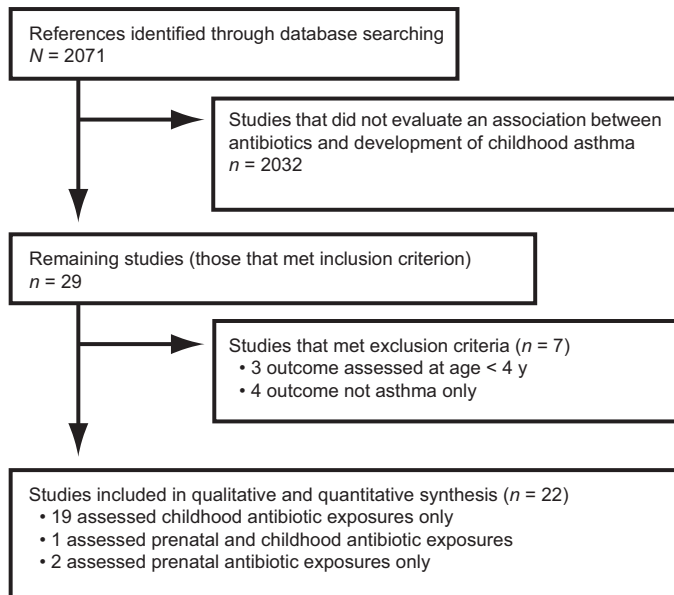


FIGURE 1

Allocation of 2071 publications identified by a PubMed search for all studies published between 1950 and July 1, 2010.

in the rest of the studies. Several included studies presented multiple estimates each for risk of asthma (ie, by conducting sensitivity or subgroup analyses); in such cases, the estimate that was judged to be the least susceptible to bias while retaining the most statistical power was included in the meta-analysis. A detailed list of all estimates eligible for inclusion, as well as rationale for selecting the estimate that was used, are provided in [Supplemental Table 5](#) (early life exposures) and [Supplemental Table 6](#) (in utero exposures).

Exposure to Antibiotics in the First Year of Life and Risk of Childhood Asthma

Study-specific and pooled risk estimates of asthma after any exposure to antibiotics in the first year of life are provided in Fig 2. The pooled OR for the adjusted estimates of all 20 applicable studies was 1.52 (95% CI: 1.30–1.77). However, this estimate showed high heterogeneity ($P = 95\%$), which supports the need for subgroup analysis. For the main subgroup analysis, studies were analyzed according to design

type (viz, retrospective, database, or prospective). Retrospective studies ($n = 8$) showed the highest pooled estimate of any subgroup (pooled OR: 2.04 [95% CI: 1.83–2.27]). These studies contributed significantly to the heterogeneity among all included studies while having moderate intragroup heterogeneity ($P = 45\%$). Database studies had a significantly weaker pooled estimate ($n = 6$; OR: 1.35 [95% CI: 1.12–1.62]) (test for interaction, retrospective versus database subgroup: $P = .0001$). Prospective studies revealed the weakest pooled estimate, which revealed no significant effect of antibiotics on asthma ($n = 6$; OR: 1.07 [95% CI: 0.89–1.28]) (retrospective or database versus prospective subgroup: $P < .000001$ and $P = .075$, respectively). However, prospective studies were small (total cohort size: 5133 subjects) compared with the total database cohort size (400 167 subjects). Significant heterogeneity was detected among database studies ($P = 96\%$) but not prospective studies ($P = 0\%$).

To further investigate heterogeneity according to factors other than study design, sensitivity analyses were performed by using prospective and database studies combined (retrospective studies were excluded because of the clear effect on heterogeneity, as discussed in the previous section). The main findings for the sensitivity analyses are provided in Fig 3, and [Supplemental Table 7](#) summarizes all sensitivity analyses in detail. The pooled OR for prospective and database studies combined was 1.25 (95% CI: 1.08–1.45; $P = 92\%$; $n = 12$). Stratifying this group according to age of first possible asthma incidence revealed that studies with asthma at ages 0 to 1 year had a higher pooled estimate ($n = 9$; OR: 1.26 [95% CI: 1.08–1.47]; $P = 51\%$) than those with asthma at ages 2 to 3 ($n = 3$; OR: 1.16 [95% CI: 1.06–1.25]; $P = 43\%$), although this difference was not significant. This effect was driven by database studies, because there were no prospective studies that assessed asthma at the age of 2 years or older. Stratifying according to adjustment or no adjustment for respiratory infections revealed that studies that did not adjust had a higher pooled estimate ($n = 7$; OR: 1.38 [95% CI: 1.15–1.65]; $P = 64\%$) than those that did adjust ($n = 5$; OR: 1.16 [95% CI: 1.08–1.25]; $P = 30\%$) (test for interaction: $P = .079$). This result was also observed when restricted to database studies but not when restricted to prospective studies. Figure 3B provides a Galbraith plot that illustrates study heterogeneity when stratifying according to adjustment for respiratory infections. Note that the 2 largest studies, by Martel et al⁴⁰ and Marra et al,³⁹ strongly influenced study heterogeneity and the results of the stratification analyses. Although both of them were large database studies, Martel et al⁴⁰ examined asthma at age 0 or older, did not adjust for respiratory infections, and reported a relatively strong

TABLE 1 Characteristics of the Least Biased Estimates From Included Studies That Assessed Antibiotic Exposure in the First Year of Life and Risk of Childhood Asthma ($n = 20$)

Source (Year)	Study Design	Population	No. of Cases/Total	Exposure	Indication for Antibiotic Use	Respiratory Infections in Early Life	Exposure Assessment Method	Asthma Definition	Outcome
Ponsonby et al ⁴² (1999)	Prospective cohort	Children born in 1 of 6 obstetric hospitals in Tasmania, Australia	276/856	Any antibiotic use, ages 0–1 y	Not adjusted for	Not adjusted for	Self-report, within 1 y after birth	Self-report, positive response to “has your child ever had asthma?”	Ever asthma at ages 6–7 y
Wickens et al ⁴⁶ (1999)	Retrospective	Children attending 1 of 6 Rudolf Steiner schools in New Zealand	27/217	Any antibiotic use, ages 0–1 y	Not adjusted for	Not adjusted for	Self-report, 5–10 y after birth	Self-report, positive response to “has your child ever had asthma?”	Ever asthma at ages 5–10 y, excluding those with symptoms at ages 0–1 y
Droste et al ³² (2000)	Retrospective	Children attending schools in urban and residential communities in or near Antwerp, Belgium	53/1180	Any antibiotics, ages 0–1 y	Not adjusted for	Adjusted for LRIs	Self-report, 6–7 y after birth	Self-report, positive response to “has your child ever had asthma?”	Ever asthma at ages 7–8 y, excluding those with symptoms at ages 0–1 y
Wjst et al ⁴⁷ (2001)	Retrospective	Schoolchildren in Sachsen-Anhalt, Germany	Unclear for selected estimate	Any antibiotic use, ages 0–1 y	Estimate is for nonpulmonary indications	Not adjusted for	Self-report, 5–14 y after birth	Self-report, positive response to “did a physician ever notice asthma or asthma-like bronchitis?”	Ever asthma at ages 5–14 y
Celedón et al ³⁰ (2002)	Prospective	Children with a history of allergy or asthma in at least 1 parent, recruited in Boston, MA	38/448	Antibiotics, ages 0–1 y	Reported, but not adjusted for	Not adjusted for	Self-report, every 2 mo from birth to 1 y of age	Self-report, physician-diagnosed asthma with ≥ 1 wheezing episode in the past 12 mo	Current asthma at ages 4–5 y
McKeever et al ⁴¹ (2002)	Database	Children in the United Kingdom in the West Midlands General Practice Research database, registered with a physician within 3 mo of birth and had at least 1 consultation	2948/21 129	Antibiotics, by type, ages 0–1 y	Not adjusted for	Not adjusted for	Database codes for antibiotic prescriptions	Database codes for at least 1 asthma diagnosis	Incident asthma at ages 1–9 y
Celedón et al ²⁸ (2004)	Database	Children enrolled from birth to 5 y of age in a health maintenance organization in Boston, MA	314/4178	Antibiotics, by type, ages 0–1 y	Not adjusted for	Adjusted for LRIs (and URIs separately)	Database codes for antibiotic prescriptions	Database codes for > 1 ambulatory visit or at least 1 emergency department visit/hospitalization for asthma, or for > 1 antiasthma medication prescription	Current asthma at ages 4–5 y (incident at ages 2–5 y)
Cohet et al ³¹ (2004)	Retrospective	Children with notifiable infectious diseases (38% of cohort) in New Zealand and a general population of schoolchildren (62%) from 85 schools in Wellington, New Zealand	1277/3927	Any antibiotics, ages 0–1 y	Not adjusted for	Not adjusted for	Self-report, 6–7 y after birth	Self-report, positive response to “has your child ever had asthma?”	Ever asthma at ages 6–7 y
Ahn et al ²⁸ (2005)	Retrospective	Children attending 1 of 29 randomly selected urban and rural schools in South Korea	2354/25 990	Antibiotics, ages 0–1 y	Not adjusted for	Not adjusted for	Self-report by mother, 7–12 y after birth	Self-report, positive response to “has your child ever had asthma?”	Ever asthma at ages 7–12 y
Floistrup et al ³³ (2006)	Retrospective	Children attending Steiner and non-Steiner schools in 5 European countries	636/6630	Any antibiotics, ages 0–1 y	Not adjusted for	Not adjusted for	Self-report by parents, 5–13 y after birth	Self-report, ever diagnosed with asthma, or obstructive bronchitis more than once	Ever asthma at ages 5–13 y
Kozynskyj et al ³⁶ (2007)	Database	Children born in Manitoba, Canada, and continuously registered with the Manitoba Health Services insurance plan from 1995 to 2003	787/13 116	Antibiotics, by type, ages 0–1 y	Included a separate analysis of antibiotics for nonrespiratory infections (see Supplemental Table 5)	Adjusted for LRIs (and URIs separately)	Database codes for antibiotic prescriptions	Database codes for > 1 physician visit for asthma or at least 1 asthma hospitalization, or for > 1 antiasthma medication prescription	Current asthma at ages 7–8 y, excluding subjects diagnosed at ages 0–1 y

TABLE 1 Continued

Source (Year)	Study Design	Population	No. of Cases/Total	Exposure	Indication for Antibiotic Use	Respiratory Infections in Early Life	Exposure Assessment Method	Asthma Definition	Outcome
Kusel et al ⁵⁷ (2008)	Prospective	Children with at least 1 parent with doctor-diagnosed asthma, hay fever, or eczema, from a study conducted in Australia	37/198	At least 2 prescriptions of the same antibiotic within 7 d of each other, ages 0–1 y	Reported, but not adjusted for	Not directly adjusted for but used an adjustment for antibiotic propensity	Self-report, daily log-book entries from birth to 5 y of age	Self-report of history of doctor-diagnosed asthma with current wheeze	Current asthma at ages 4–5 y
Wickens et al ⁴⁵ (2008)	Prospective	Mothers recruited into the New Zealand Asthma and Allergy Cohort Study through a random sample of midwives between 1997 and 2001	Unclear/847	Any antibiotic use, ages 0–15 mo	Not adjusted for	Adjusted for chest infections	Self-report 3 and 15 mo after birth	Self-report, positive response to “has your child ever had asthma?”	Current asthma at ages 3–4 y, excluding subjects with asthma before 15 mo of age
Foliaki et al ⁵⁴ (2009)	Retrospective	Children attending randomly selected schools in 29 countries	Unclear/103 653	Any antibiotics, ages 0–1 y	Not adjusted for	Not adjusted for	Self-report, 6–7 y after birth	Self-report, positive response to “has your child ever had asthma?”	Ever asthma at ages 6–7 y
Marra et al ⁵⁹ (2009)	Database	All live births in British Columbia, Canada, from 1997 to 2003 with at least 2 y of follow-up after birth	18 864/251 817	Antibiotics, ages 0–1 y	Included analysis of antibiotics for nonrespiratory infections (see Supplemental Table 5)	Adjusted for LRIs and URIs	Database codes for antibiotic prescriptions	Database codes for at least 1 asthma hospitalization, 2 medical claims for asthma within 12 mo, or 2 antiasthma medication prescriptions within 12 mo	Incident asthma at ages 2–9 y
Martel et al ⁴⁰ (2009)	Database	Children of mothers in administrative health databases in Quebec, Canada, who had at least 1 pregnancy during the study period	Main analysis: 5226/109 746; subgroup analysis: 935/19 635	Any antibiotics, ages 0–6 mo	Not adjusted for	Not adjusted for	Database codes for antibiotic prescriptions	Database codes for at least 1 asthma diagnosis and at least 1 antiasthma medication prescription within 2 y	Main analysis: incident asthma at ages 0–10 y; subgroup analysis: incident asthma at ages 3–10 y
Karimi et al ⁵⁵ (2009)	Retrospective	Schoolchildren in Yazd, Iran	49/1455	Any antibiotics, ages 0–1 y	Not adjusted for	Not adjusted for	Self-report, 6–7 y after birth	Self-report, positive response to “has your child ever had asthma?”	Ever asthma, ages 6–7 y
Mai et al ⁵⁸ (2010)	Prospective	Infants born between 1994 and 1996 in Stockholm, Sweden	Unclear for selected estimate/2424	Any antibiotics, ages 0–1 y	Not adjusted for	Adjusted for pneumonia and bronchitis at ages 0–1 y	Self-report, 1 y after birth	Self-report of asthma, defined as ≥ 3 wheezing episodes or 1 wheezing episode combined with inhaled glucocorticoids for asthma or asthma symptoms in the past 12 mo	Current asthma, age 4 y, excluding children with asthma in the first year of life
Sobko et al ⁴⁵ (2010)	Database (for exposure assessment)	Children and adolescents born in Stockholm, Sweden, who received antibiotics, and age- and gender-matched controls	40/201	Any use of antibiotics in the neonatal period, defined as at least 4 doses of penicillin or aminoglycoside	Not adjusted for	Not adjusted for	Database codes for antibiotic prescriptions	Self-report, positive response to “has your child ever had asthma?”	Ever asthma at ages 7–23 y
Su et al ⁴⁴ (2010)	Prospective	Infants born to women recruited during prenatal visits to obstetric and midwife practitioners in Tucson, AZ	39/360	Any antibiotic use, ages 0–9 mo	Not adjusted for	Not adjusted for	Self-report, 0–9 mo after birth	Self-report of doctor-diagnosed asthma	Current asthma at age 5 y

Characteristics listed may only be reflective of the estimate selected for the current meta-analysis and may not reflect the characteristics of the overall cohort analysis from any given study (see Supplemental Table 5 for details). LRI indicates lower respiratory infection; URI, upper respiratory infection.

TABLE 2 Characteristics of included studies assessing antibiotic exposure in utero and risk of childhood asthma ($n = 3$)

Source	Study Design	Population	No. of Cases/Total	Exposure	Exposure Assessment Method	Outcome	Outcome Definition
Benn et al ⁴⁸ (2002)	Prospective	Children of mothers who attended a prenatal care clinic at Odense University Hospital, Odense, Denmark	93/2742	Any antibiotics during pregnancy	Self-report, at 30 wk gestation and at birth	Current asthma at ages 4–5 y	Database codes for ≥ 3 antiasthma medication prescriptions, in a prescription-refunds database
McKeever et al ⁴⁹ (2002)	Database	Children in the United Kingdom in the West Midlands General Practice Research database, registered with a physician within 3 mo of birth and had at least 1 consultation	2671/24 690	Any antibiotics during pregnancy	Database codes for antibiotic prescriptions	Incident asthma at ages 0–10 y	Database codes for at least 1 asthma diagnosis
Martel et al ⁴⁰ (2009)	Database	Children of mothers in administrative health databases in Quebec, Canada, who had at least 1 pregnancy during the study period	5226/109 746	Antibiotics (determined by No. of prescriptions during pregnancy)	Database codes for antibiotic prescriptions	Incident asthma at ages 0–10 y	Database codes for at least 1 asthma diagnosis and at least 1 antiasthma medication prescription within 2 y

Characteristics listed may only be reflective of the estimate selected for the current meta-analysis and may not reflect the characteristics of the overall cohort analysis from any given study.

estimate (RR: 1.59 [95% CI: 1.50–1.68]), whereas Marra et al³⁹ examined asthma at the age of 2 years or older, adjusted for respiratory infections, and reported a relatively weak estimate (HR: 1.12 [95% CI: 1.08–1.16]). Note that Martel et al⁴⁰ included a subgroup analysis of subjects with asthma at the age of 3 years or older and found a weaker effect estimate (OR: 1.29 [95% CI: 1.12–1.49]) than their main analysis of asthma (Supplemental Table 5); this subgroup was used as the estimate for the Martel et al⁴⁰ study when sensitivity analyses for asthma diagnosis age were performed.

Subgrouping the studies by use of doctor-diagnosed asthma, adjustment for number of medical consultations in the first year of life, or adjustment for family history of asthma did not produce any clear differences in pooled effect estimates (Supplemental Table 7). Among database studies, those that used an RR or HR effect estimate type generally had higher pooled estimates than those that used OR estimates (Supplemental Table 7).

Two of the prospective studies, by Celedón et al³⁰ and Kusel et al,³⁷ recruited exclusively “high-risk” children with a family history of allergic disease. The pooled OR for these studies was 0.79 (95% CI: 0.48–1.28; $P = 0\%$) (Supplemental Table 7). The pooled OR for other (non–high-risk) prospective studies was 1.12 (95% CI: 0.92–1.36; $P = 0\%$), although this difference was not significant.

Funnel-plot inspection did not reveal evidence of publication bias when all studies were included (Supplemental Fig 6). Likewise, Egger’s test for asymmetric distributions did not detect significant publication bias when considering all studies ($P = .19$), retrospective studies ($P = .13$), database studies ($P = .52$), and prospective studies ($P = .77$).

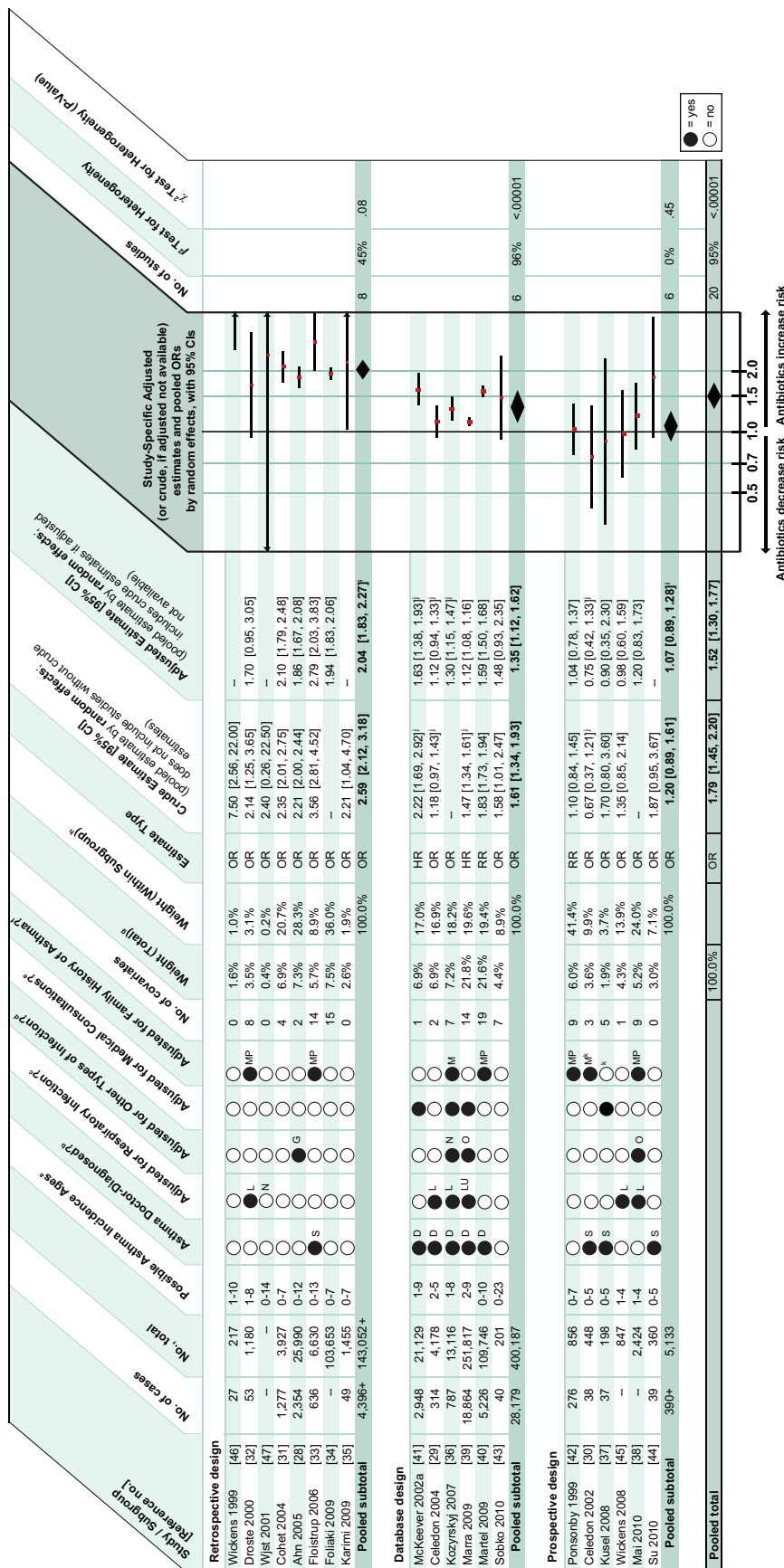


FIGURE 2

Association between any exposure to antibiotics in early life and risk of childhood asthma. Studies were initially grouped according to design type (retrospective, database, or prospective). If a study presented > 1 estimate for the association between antibiotic use and childhood asthma, the estimate that was judged to be the least biased and have the greatest power was extracted and presented here (see "Methods"). ^a Ages of first possible diagnosis and/or symptoms of asthma in cohort; ^b outcome diagnosed by a doctor (S, self-reported doctor diagnosis; D, doctor diagnosis determined from a database) or not (ie, parental report of the child "having asthma"); ^c outcome adjusted or not for respiratory infections at least in the first year of life (L, adjusted for lower respiratory infections; U, adjusted for upper respiratory infections; N, antibiotic use was for nonpulmonary indications); ^d outcome adjusted for other infections (G, gastroenteritis; O, otitis media; N, nonrespiratory infections); ^e outcome adjusted or not for number of medical consultations at least in the first year of life; ^f outcome adjusted or not for family history of asthma (M, maternal asthma; P, paternal asthma); ^g study weight, by inverse variance of the effect estimate, for the pooled estimate of all studies ($n = 20$); ^h study weight within the subgroup only for the adjusted (or crude, if adjusted not available) estimate; ⁱ pooled estimate includes crude estimates when adjusted estimate was not provided; ^j estimate derived from a pooled estimate of dose-specific estimates when estimates of any dose versus none were not directly provided (except the Marra et al.³⁹ crude, which is a pooled estimate of crude age strata); ^k the study used a cohort of children who had at least 1 parent with allergic disease. Case or total numbers are missing (—) for studies that did not present these data for the specific estimate that is listed. + indicates number sums that are less than actual because of missing data.

A

Subgroup	References Included in Each Group	No. of Studies	No. of Cases	No., Total	Heterogeneity		Pooled OR [95% CI] (FE)	Pooled OR [95% CI] (RE)	Pooled Subgroup (RE) Interaction Test, P
					I^2	$\chi^2 P$			
Prospective design	[30, 37, 38, 42, 44, 45]	6	390+	5,133	0%	.45	1.07 [0.89, 1.28]	1.07 [0.89, 1.28]	
By adj. for respiratory infections									
Not adj. for respiratory infections	[30, 37, 42, 44]	4	390	1,862	29%	.24	1.04 [0.83, 1.31]	1.05 [0.77, 1.45]	
Adj. for respiratory infections	[38, 45]	2	—	3,271	0%	.51	1.11 [0.83, 1.49]	1.11 [0.83, 1.49]	.075
Database design	[29, 36, 39 - 41, 43]	6	28,179	400,187	96%	<.0001	--	1.35 [1.12, 1.62]	
By age of asthma incidence									
Incident asthma at 0-1 y	[36, 41, 43]	3	3,775	34,446	56%	.10	1.41 [1.28, 1.55]	1.44 [1.21, 1.72]	
Incident asthma at 2-3 y	[29, 39, 40] ^a	3	20,113	275,630	0%	.99	1.13 [1.09, 1.17]	1.16 [1.06, 1.25]	.028
By adj. for respiratory infections									
Not adj. for respiratory infections	[40, 41, 43]	3	8,214	131,076	0%	.92	1.59 [1.51, 1.68]	1.59 [1.51, 1.68]	
Adj. for respiratory infections	[29, 36, 39]	3	19,965	269,111	62%	.07	1.13 [1.10, 1.17]	1.17 [1.06, 1.29]	<.0001
Prospective and database design	[29, 30, 36 - 45]	12	28,569+	405,320	92%	<.0001	--	1.25 [1.08, 1.45]	
By age of asthma incidence									
Incident asthma at 0-1 y	[30, 36 - 38, 41 - 45]	9	4,165+	39,579	51%	.04	1.32 [1.22, 1.44]	1.26 [1.08, 1.47]	
Incident asthma at 2-3 y	[29, 39, 40] ^a	3	20,113	275,630	43%	.17	1.13 [1.09, 1.17]	1.16 [1.06, 1.25]	.34
By adj. for respiratory infections									
Not adj. for respiratory infections	[30, 37, 40 - 44]	7	8,604	132,938	64%	.01	1.56 [1.48, 1.64]	1.38 [1.15, 1.65]	
Adj. for respiratory infections	[29, 36, 38, 39, 45]	5	19,965+	272,382	30%	.22	1.13 [1.10, 1.17]	1.16 [1.08, 1.25]	.079

B

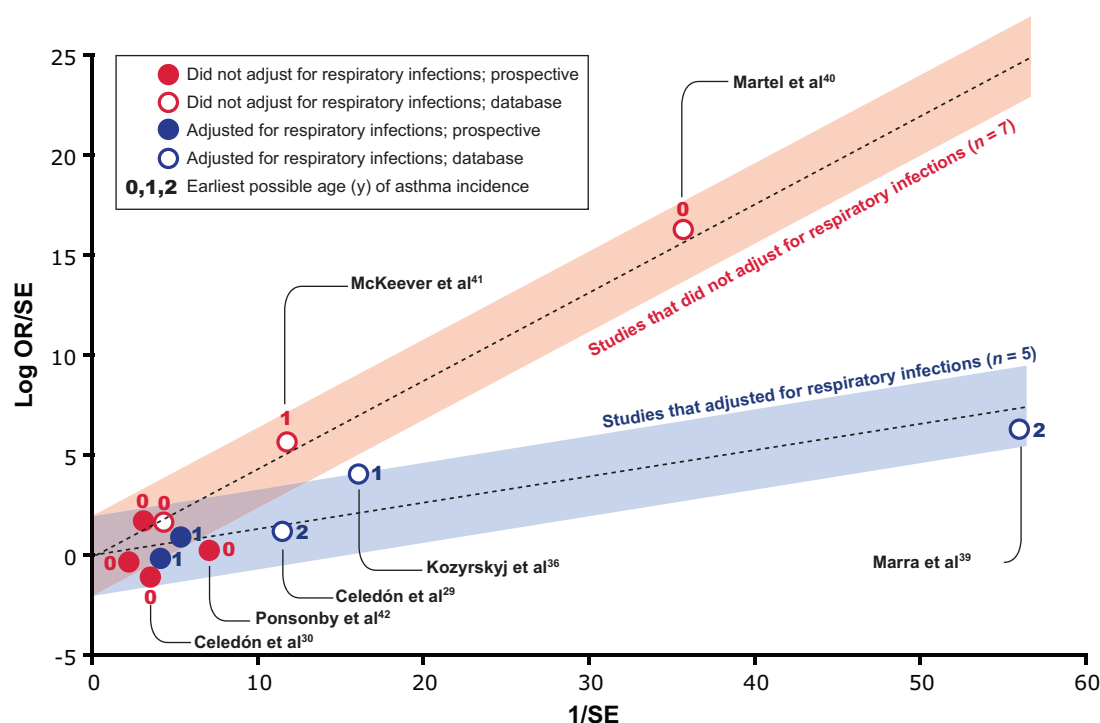


FIGURE 3

Investigation of heterogeneity among studies that assessed the association between early-life antibiotics and asthma. A, Sensitivity analysis of nonretrospective studies to identify sources of heterogeneity. Studies are first stratified according to design type (prospective, database, or both) and then to age of asthma incidence or adjustment for respiratory infections. Fixed-effects pooled estimates were not calculated when a subgroup showed high heterogeneity ($I^2 > 75\%$). ^a Estimate is for the age 3+ subgroup of Martel et al⁴⁰ (see Supplemental Table 5), used here for the analyses of stratification according to diagnosis age; when not indicated (ie, for other stratifications), the main analysis from Martel et al⁴⁰ was used. FE indicates fixed-effects model; RE, random-effects model. B, Superimposed Galbraith plots of prospective/database studies stratified according to adjustment for respiratory infections (blue) or no such adjustment (red). The slope of each regression line represents the magnitude of effect of a pooled analysis of studies in each stratum; shaded areas indicate 2 SDs above and below the regression lines. In the absence of significant heterogeneity, 95% of the included studies are expected to lie within this interval. Studies are also characterized by prospective versus database design and by age of first possible asthma incidence. Studies that fell outside of the confidence bounds of at least 1 stratum (even if not included in the regression analysis of that stratum) are indicated by reference identity.

Analysis of Dose-Specific Exposure to Antibiotics in Early Life and Risk of Asthma

Ten studies that assessed the risk of asthma after early-life expo-

sure to antibiotics included estimates by number of courses of antibiotics.^{28–30,36–39,41,44,46} Five of these studies^{28,29,36,39,41} allowed comparisons of 1 to 2, 3 to 4, and >4 courses versus

none (Fig 4). Pooled ORs of these studies revealed that there was a stronger risk of asthma for increased numbers of doses. However, when the study by Ahn et al²⁸ (the only ret-

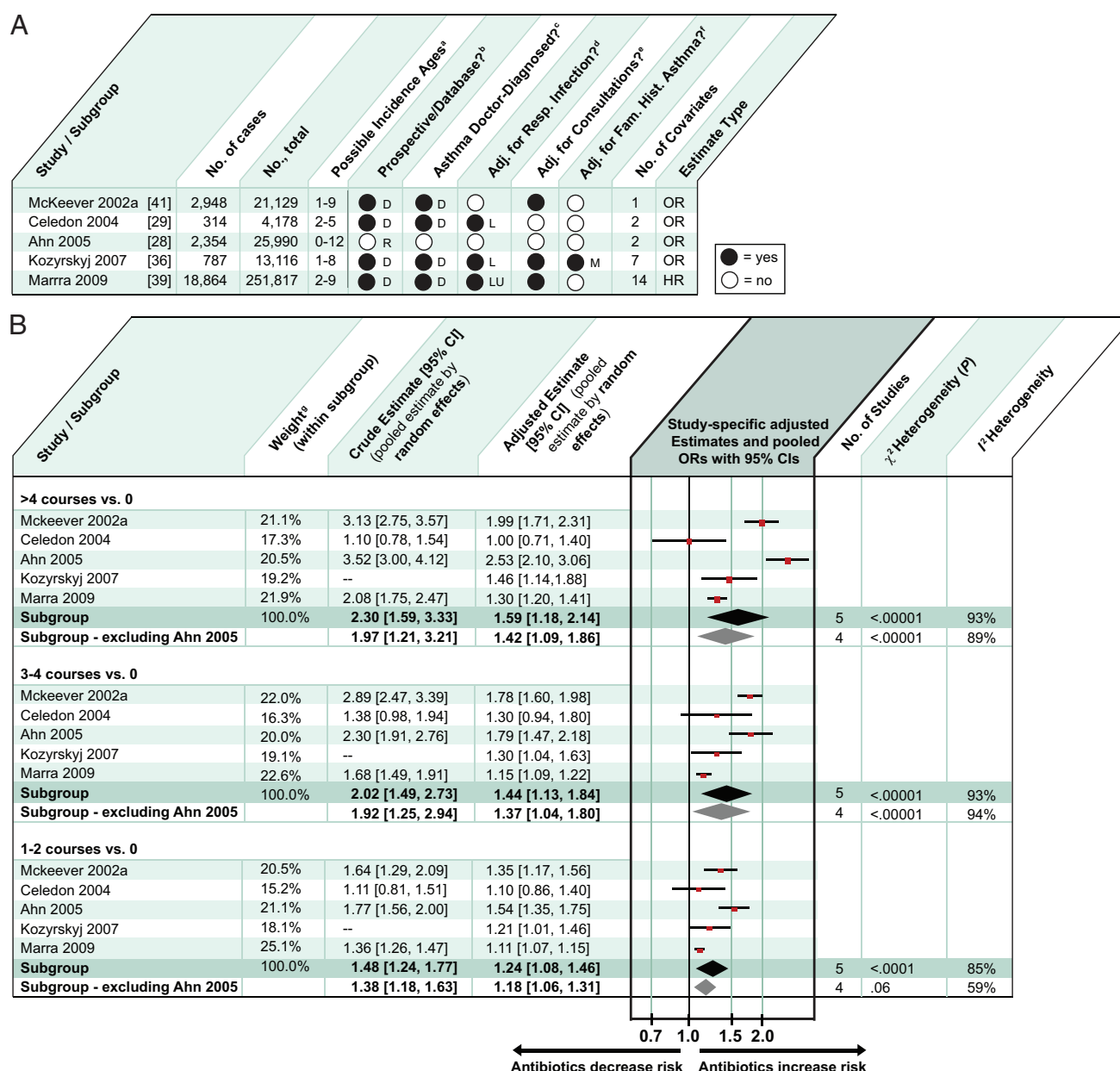


FIGURE 4

Dose-effect assessment for antibiotics in early life and risk of childhood asthma. A, Study characteristics; B, study-specific and pooled effect estimates according to number of courses of antibiotics. ^a Ages of first possible diagnosis and/or symptoms of asthma in cohort; ^b design methodology used to assess exposure (R, retrospective; D, database); ^c outcome diagnosed by a doctor (D, doctor diagnosis determined from a database) or not (ie, parental report of the child "having asthma"); ^d outcome adjusted or not for respiratory infections at least in the first year of life (L, adjusted for lower respiratory infections; U, adjusted for upper respiratory infections); ^e outcome adjusted or not for number of medical consultations at least in the first year of life; ^f outcome adjusted or not for family history of asthma (M, maternal asthma); ^g study weight by inverse variance of the effect estimate for the pooled estimate of each dose group ($n = 5$).

rospective study) was removed, the pooled estimates for >4 and 3 to 4 courses were nearly the same. No pairwise comparison with the 1- to 2-course subgroup showed a significant test for interaction for either analysis.

Five additional studies^{30,37,38,44,46} examined dose-specific effects but did not have directly comparable strata. When combined into strata with the previous 5 studies ($n = 10$), the pooled OR for assessment of >1 vs 0 or >2 courses vs 0 was 1.49 (95% CI: 1.24–1.80; $P =$

76%), whereas the pooled OR for assessment of 1 course vs 0 or 1 to 2 courses vs 0 was 1.24 (95% CI: 1.10–1.40; $P = 72\%$) (test for interaction: $P = .11$). When the 2 retrospective studies were removed (Wickens et al⁴⁶ and Ahn et al²⁸) ($n = 8$), these pooled

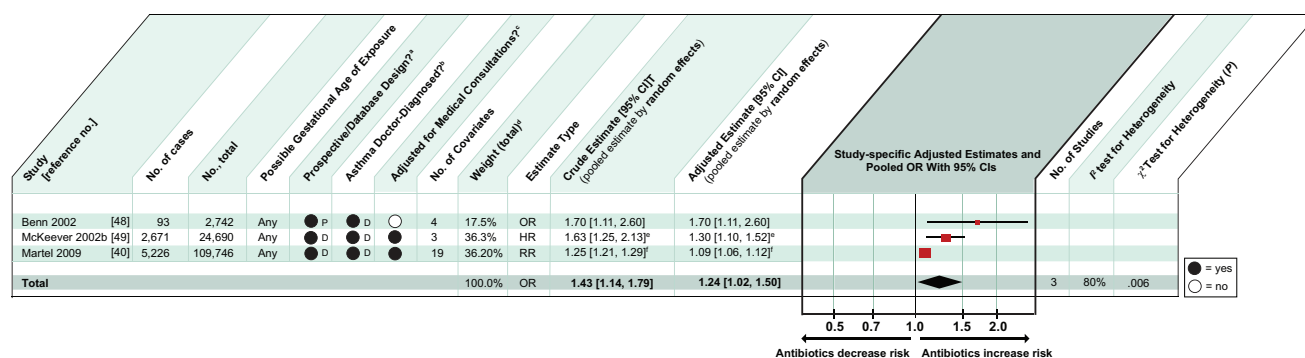


FIGURE 5

Association between exposure to antibiotics during pregnancy and risk of childhood asthma. ^a Design methodology used to assess exposure (P, prospective; D, database); ^b outcome diagnosed by a doctor (D, doctor diagnosis determined from a database); ^c outcome adjusted or not for number of medical consultations at least in the first year of life; ^d study weight by inverse variance of the effect estimate for the pooled estimate ($n = 3$); ^e estimate derived from a pooled estimate of exposure dose-specific estimates for which estimate of any versus no exposure was not directly provided; ^f estimate is the RR per additional antibiotic prescription, because an estimate of any versus none was not provided.

estimates became 1.37 (95% CI: 1.14–1.65; $P = 74\%$) and 1.15 (95% CI: 1.08–1.23; $P = 20\%$), respectively (test for interaction: $P = .08$).

Exposure According to Type of Antibiotics and Risk of Asthma

Four studies assessed the effect of type of antibiotic on the association between exposure in the first year of life and childhood asthma, but because of high heterogeneity they could not be meta-analyzed. McKeever et al⁴¹ reported that although amoxicillin, macrolides, cephalosporins, and augmentin were all associated with a significantly increased risk of asthma, no risk with penicillin was revealed. In contrast, Marra et al³⁹ reported that penicillin exposure was associated with a relatively high risk for asthma and that amoxicillin, macrolides, cephalosporins, and sulfonamide were also significantly associated with asthma, whereas all other types of antibiotics were not. Kozyrskyj et al³⁶ grouped antibiotics into categories of “narrow-spectrum” (penicillin, cloxacillin, cephalexin, cefadroxil, and erythromycin) and “broad-spectrum” (all other classes) antibiotics and found that the OR for narrow-spectrum antibiotics was 1.35 (95% CI: 0.29–6.23), whereas for broad-spectrum antibiotics the OR

was 1.50 (95% CI: 1.16–1.93). Finally, Celedón et al²⁹ reported that there was no association according to any class of antibiotic.

Exposure to Antibiotics During Pregnancy and Risk of Asthma

Three studies assessed whether exposure to antibiotics in pregnancy was associated with childhood asthma (Fig 5). The pooled estimate for these studies revealed an increased risk with borderline significance (pooled OR: 1.24 [95% CI: 1.02–1.50]; $P = 80\%$). The only prospective study had the highest effect estimate (OR: 1.70 [95% CI: 1.11–2.60]) compared with the other 2 studies, which were of database design (pooled OR of the 2 database studies: 1.38 [95% CI: 1.07–1.77]; $P = 73\%$). The 2 studies that did not adjust for medical consultation rates had a higher pooled estimate (pooled OR: 1.65 [95% CI: 1.32–2.07]; $P = 0\%$) than the study that did (RR: 1.09 [95% CI: 1.06–1.12]). The estimate for this latter study, Martel et al,⁴⁰ is the RR per each additional antibiotic prescription, which may explain the smaller effect estimate.

DISCUSSION

With this review we aimed to determine if exposure to antibiotics during pregnancy or in early life increased

the risk for childhood asthma. On the basis of the heterogeneity analysis, nonretrospective studies that adjusted for respiratory infections likely had the greatest validity in assessing early-life exposures. The pooled estimate of effect for these studies (OR: 1.13 [95% CI: 1.10–1.17]; $n = 5$; fixed effects) is also in general agreement with stratification according to studies that only examined asthma at the age of 2 years or older (pooled OR: 1.13 [95% CI: 1.09–1.17]; $n = 3$; fixed effects), which suggests that there is a significant but weak association between antibiotic use in early life and childhood asthma.

Assuming a baseline childhood asthma incidence rate of 10%, an OR of 1.13 (95% CI 1.10–1.17) yields a number needed to harm of 87 (95% CI: 67–113); that is, for every 87 children exposed to antibiotics, 1 child will develop asthma because of his or her antibiotic exposure. However, this number is highly uncertain, because it is sensitive to the assumptions that were used to generate the effect estimate. Nevertheless, if there is a true causal relation between antibiotics and asthma, the total number of children who develop asthma as a result of this exposure is not insignificant even for small effect esti-

mates, given the large proportion of children who are exposed to antibiotics.

We took 2 approaches in attempting to reduce the effect of protopathic bias: (1) stratifying studies according to their adjustment or lack of adjustment for respiratory infections; and (2) stratifying studies according to their age of first possible asthma diagnosis (age 0 or 1 vs ≥ 2 years). With both of these stratifications we were able to reduce the heterogeneity among the combined prospective and database studies, and studies that did not adjust for respiratory infections or used earlier ages of asthma incidence revealed a stronger relationship between antibiotic exposure and asthma, which supports the interpretation that protopathic bias was present among such studies. However, protopathic bias likely does not completely explain the observed association between antibiotics and asthma, because pooled estimates of studies with older ages of asthma incidence and those that adjusted for respiratory infections retained significant risk estimates. This insufficiency of protopathic bias to completely account for the association is emphasized by the Marra et al study,³⁹ in which 2 sensitivity analyses were conducted: 1 that examined antibiotics not dispensed for respiratory infections or otitis media in the first year of life, which revealed that the association with asthma at ages 2 through 9 years was retained (HR: 1.13 [95% CI: 1.09–1.16]), and 1 that excluded children diagnosed with respiratory infections or otitis in the first year, which also revealed that the association was retained (HR: 1.17 [95% CI: 1.10–1.25]).

Retrospective studies (with self-reported exposure) revealed the highest pooled risk estimate of any subgroup, which strongly suggests recall bias. Conversely, all nonsignificant estimates of asthma risk were reported by prospective studies, which may be a result of the relatively small number of

subjects in the prospective studies compared with the database studies. Moreover, it has been suggested that antibiotic use is not a risk factor in children with a genetic predisposition to asthma,^{17,36} which could explain the lack of an association in 2 of the prospective studies that exclusively studied children with a family history of allergic disease. To explore the effect of familial history of asthma, we conducted a subgroup analysis that revealed that, although the association was “protective” in the high-risk studies and harmful in the other prospective studies, the low numbers of participants yielded low precision, and we found no statistical difference between the 2 groups. The uncertainty of subgroup effects by parental asthma, therefore, challenges the interpretation of the lack of an association in the prospective study group.

Database studies included in this review mostly showed significant associations, but this study design may be vulnerable to recall biases in their original data collection and susceptible to detection bias, as well as other potential limitations.⁵⁰ Because evidence of a significant association between antibiotics and asthma in the reviewed literature is entirely supported by retrospective and database studies, the conclusion that there is a causal relationship between antibiotics and asthma should be treated with caution until large, prospective studies can be conducted to examine this question.

For the 3 studies of in utero antibiotic exposure, the pooled estimate revealed a significantly increased risk of asthma, which supports an etiologic relation between antibiotic use and asthma, because reverse causality and protopathic bias are inherently avoided in this exposure. However, these studies may still be susceptible to sources of confounding such as pre-

maturity, chorioamnionitis, and maternal smoking, all of which may be associated with antibiotic use during pregnancy and asthma or wheezing in children.^{51,52} Although Benn et al⁴⁸ and Martel et al⁴⁰ adjusted for low gestational age and small-for-gestational age, respectively, the McKeever et al⁴⁹ study had no similar adjustment. In addition to chorioamnionitis, other types of maternal infections have also been associated with increased asthma risk in the child,^{49,53} which makes it difficult to disentangle the independent effects of antibiotics and infections, although the study by McKeever et al⁴⁹ found that prenatal antibiotics significantly increased the risk for asthma even after adjusting for the number of maternal infections. Other sources of bias, including detection bias, may also remain. Intrapartum antibiotics, such as used for group B streptococcus prophylaxis, have been suggested to be another exposure source that could influence the risk of asthma,⁵⁴ but investigation of this relationship remains underdeveloped in the literature and was not included in our review.

A primary strength of our systematic review is our focus on minimizing the most likely sources of bias that confound the relation between antibiotics and asthma, including subgrouping analyses according to study design, age of asthma diagnosis, and adjustment for respiratory infections. Limitations include the possibility that analyzing longer “wash-out” periods (ie, by using later ages of asthma diagnosis) between antibiotic exposure and asthma may overcompensate for protopathic bias, because it is possible that a true etiologic relation between antibiotic exposure and asthma may be more likely to occur on a shorter time scale than can be assessed by waiting until the age of 2 years or older to determine outcome. Moreover, fully

adjusted effect estimates from most studies may have “overadjusted” the pooled estimate compared with what the true estimate should be.

A previous systematic review on childhood antibiotic exposure and asthma (by Marra et al¹⁷) included 8 studies in its meta-analysis. Our review included all of the studies from the previous review, except 1 that did not meet the criteria of exposure,²² together with an additional 13 studies for early-life exposure. The main conclusions of our review are in agreement with those of

Marra et al¹⁷, who found that retrospective studies revealed a significant relation between antibiotic use and asthma but that prospective studies did not. An important addition to this topic are the large database studies, the results of which were published subsequent to the Marra et al¹⁷ review.

CONCLUSIONS

To date, evidence suggests that antibiotic exposure in early life or in utero slightly increases the risk of developing childhood asthma. However, this conclu-

sion remains tentative, because evidence for protopathic bias was observed in the methodologically less secure studies. Future studies of large, prospective cohorts that adequately address concerns for protopathic bias are needed to definitively address this question.

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Prenatal or Early-Life Exposure to Antibiotics and Risk of Childhood Asthma: A Systematic Review

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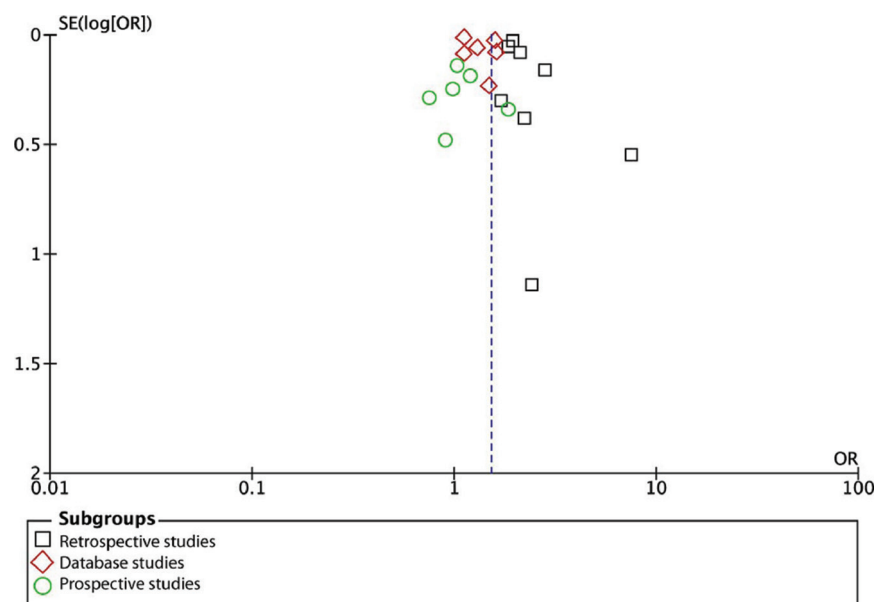
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Supplemental Information



SUPPLEMENTAL FIGURE 6

The funnel plot does not show evidence of publication bias for the totality of studies (analysis of any exposure to antibiotics in the first year of life and risk of childhood asthma).

SUPPLEMENTAL TABLE 3 PRISMA 2009 Checklist

Section/Topic	No.	Checklist item	Reported in
Title			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Page 1
Abstract			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	Page 1
Introduction			
Rationale	3	Describe the rationale for the review in the context of what is already known.	Introduction, paras 1–2
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	Introduction, para 3
Methods			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (eg, Web address), and, if available, provide registration information including registration number.	Methods, para 1
Eligibility criteria	6	Specify study characteristics (eg, PICOS, length of follow-up) and report characteristics (eg, years considered, language, publication status) used as criteria for eligibility, giving rationale.	Methods, para 2
Information sources	7	Describe all information sources (eg, databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	Methods, para 2
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Methods, para 2
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Methods, para 3
Data-collection process	10	Describe method of data extraction from reports (eg, piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	Methods, para 4
Data items	11	List and define all variables for which data were sought (eg, PICOS, funding sources) and any assumptions and simplifications made.	Methods, para 4
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	Methods, para 4
Summary measures	13	State the principal summary measures (eg, risk ratio, difference in means).	Methods, para 6
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (eg, <i>I</i> ²) for each meta-analysis.	Methods, para 6
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (eg, publication bias, selective reporting within studies).	Methods, para 6
Additional analyses	16	Describe methods of additional analyses (eg, sensitivity or subgroup analyses, meta-regression), if done, indicating which were prespecified.	Methods, para 6
Results			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Results, para 1; Fig 1
Study characteristics	18	For each study, present characteristics for which data were extracted (eg, study size, PICOS, follow-up period) and provide the citations.	Table 1; Table 2
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Fig 3; Supplemental Table 7
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Figs 2–4
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Figs 2 and 4; results, paras 2–5 and 7–10
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see item 15).	Results, para 6; Supplemental Fig 3
Additional analysis	23	Give results of additional analyses, if done (eg, sensitivity or subgroup analyses, meta-regression [see Item 16]).	Fig 3; results, paras 3–7
Discussion			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (eg, health care providers, users, and policy-makers).	Discussion, para 1
Limitations	25	Discuss limitations at study and outcome level (eg, risk of bias), and at review-level (eg, incomplete retrieval of identified research, reporting bias).	Discussion, paras 2–8
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	Discussion, para 9
Funding			
Funding	27	Describe sources of funding for the systematic review and other support (eg, supply of data); role of funders for the systematic review.	Acknowledgments

Form from Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med*. 2009;6(7):e1000097. For more information, see www.prisma-statement.org.

SUPPLEMENTAL TABLE 4 Characteristics of Excluded Studies ($n = 7$)

Study	Description	Reason for Exclusion
Farooqi and Hopkin ²¹ (1998)	Retrospective cohort study of 1934 children that examined the association between asthma (at ages >2 y) and antibiotic use in the first 2 y of life (OR: 3.19 [95% CI: 2.43–4.18], any vs none)	Wrong age of exposure (ages 0–2 y)
Illi et al ²² (2001)	Prospective cohort study of 1314 children that examined the association between doctor-diagnosed asthma (ever at age 7 y) and antibiotics in the first 3 y of life (OR: 1.08 [95% CI: 0.59–1.99], ≥ 2 courses vs 1 or 0)	Wrong age of exposure (ages 0–3 y)
Karadağ et al ²³ (2007)	Cross-sectional study of 14 893 children that examined the association between atopic eczema with asthma and antibiotic use ever	Wrong outcome of interest (asthma-associated atopic eczema)
Majkowska-Wojciechowska et al ²⁴ (2007)	Cross-sectional study of 404 children that examined the association between asthma and/or atopy and antibiotic use	Wrong outcome of interest (asthma and/or atopy)
Mullooly et al ²⁵ (2007)	Case-control study of 1074 children that examined the association between asthma-associated atopy and the number of antibiotic prescriptions in the first year of life	Wrong outcome of interest (asthma-associated atopy)
Thomsen et al ²⁶ (2006)	Case-cohort study of 480 children that examined the relationship between atopic disease (hay fever and/or asthma) and antibiotics at ages 0–2 y	Wrong outcome of interest (hay fever and/or asthma)
von Mutius et al ²⁷ (2009)	Cross-sectional study of 7498 children that examined the association between asthma (ever at ages 5–11 y) and antibiotic use in the first 3 y of life (OR: 1.63 [95% CI: 1.26–2.13], 1–2 courses vs 0; OR: 7.95 [95% CI: 6.02–10.50], >5 courses vs 0)	Wrong age of exposure (ages 0–3 y)

SUPPLEMENTAL TABLE 5 List of Eligible Study Estimates and Rationale for Use in the Meta-analysis

Stratum Type	Age at Antibiotic Use	No. of Courses	Age at First Symptoms or Diagnosis	Type of Outcome	Adjusted for Respiratory Infection?	Covariates	No. of Cases/Total	Estimate (95% CI)	Location of Estimate in Article	Used in Meta-analysis? (Rationale)
Ahn et al ²⁸ (2005)										
Overall analysis ^a	0–1 y	Any	0–12 y	Ever-asthma at ages 7–12 y	No	Fever episodes, acute gastroenteritis in infancy	2354/25 990	1.862 (1.668–2.080)	Table 2	Yes (this was the only relevant adjusted estimate for exposure of any antibiotics)
According to dose ^a	0–1 y	1–2	0–12 y	Ever-asthma at ages 7–12 y	No	Fever episodes, acute gastroenteritis in infancy	2354/25 990	1.537 (1.347–1.755)	Table 4	Yes (used for dose-response analysis)
According to dose ^a	0–1 y	3–4	0–12 y	Ever-asthma at ages 7–12 y	No	Fever episodes, acute gastroenteritis in infancy	2354/25 990	1.792 (1.474–2.179)	Table 4	Yes (used for dose-response analysis)
According to dose ^a	0–1 y	>4	0–12 y	Ever-asthma at ages 7–12 y	No	Fever episodes, acute gastroenteritis in infancy	2354/25 990	2.533 (2.099–3.058)	Table 4	Yes (used for dose-response analysis)
Celedón et al ³⁰ (2002)										
According to dose ^a	0–1 y	1	0–5 y	Current asthma at age 5 y	No	Gender, income, maternal history of asthma	38/448	0.5 (0.2–1.4)	Table 2	Yes (collapsed for analysis of any exposure; also used for dose response)
According to dose ^a	0–1 y	>1	0–5 y	Current asthma at age 5 y	No	Gender, income, maternal history of asthma	38/448	0.9 (0.4–1.8)	Table 2	Yes (collapsed for analysis of any exposure; also used for dose response)
Celedón et al ²⁹ (2004)										
Adjusted for No. of office visits	0–1 y	1–2	2–5 y	Current asthma at age 5 y	No	Gender, office visits	314/4178	0.9 (0.7–1.3)	Table 3	No (estimate adjusted for office visits; considered not as relevant as LRIs)
Adjusted for No. of office visits	0–1 y	3–4	2–5 y	Current asthma at age 5 y	No	Gender, office visits	314/4178	1.0 (0.7–1.4)	Table 3	No (estimate adjusted for office visits; considered not as relevant as LRIs)
Adjusted for No. of office visits	0–1 y	>4	2–5 y	Current asthma at age 5 y	No	Gender, office visits	314/4178	0.6 (0.4–0.9)	Table 3	No (estimate adjusted for office visits; considered not as relevant as LRIs)
Adjusted for LRIs ^a	0–1 y	1–2	2–5 y	Current asthma at age 5 y	Yes	Gender, LRIs	314/4178	1.1 (0.8–1.4)	Table 3	Yes (this estimate adjusted for LRIs; collapsed for any-use analysis and used for dose response)
Adjusted for LRIs ^a	0–1 y	3–4	2–5 y	Current asthma at age 5 y	Yes	Gender, LRIs	314/4178	1.3 (0.9–1.8)	Table 3	Yes (this estimate adjusted for LRIs; collapsed for any-use analysis and used for dose response)
Adjusted for LRIs ^a	0–1 y	>4	2–5 y	Current asthma at age 5 y	Yes	Gender, LRIs	314/4178	1.0 (0.7–1.4)	Table 3	Yes (this estimate adjusted for LRIs; collapsed for any-use analysis and used for dose response)
Adjusted for LRIs	0–1 y	1–2	2–5 y	Current asthma at age 5 y	Yes	Gender, LRIs	314/4178	1.0 (0.8–1.4)	Table 3	No (estimate adjusted for LRIs; considered not as relevant as LRIs)

SUPPLEMENTAL TABLE 5 Continued

Stratum Type	Age at Antibiotic Use	No. of Courses	Age at First Symptoms or Diagnosis	Type of Outcome	Adjusted for Respiratory Infection?	Covariates	No. of Cases/Total	Estimate (95% CI)	Location of Estimate in Article	Used in Meta-analysis? (Rationale)
Adjusted for URIs	0–1 y	3–4	2–5 y	Current asthma at age 5 y	Yes	Gender, URIs	314/4178	1.2 (0.9–1.7)	Table 3	No (estimate adjusted for URIs; considered not as relevant as LRIs)
Adjusted for URIs	0–1 y	>4	2–5 y	Current asthma at age 5 y	Yes	Gender, URIs	314/4178	0.9 (0.6–1.3)	Table 3	No (estimate adjusted for URIs; considered not as relevant as LRIs)
Cohet et al ³¹ (2004) Overall analysis ^a	0–1 y	Any	0–7 y	Ever-asthma at ages 6–7 y	No	Data set (general population vs population with notifiable infectious diseases), gender, family size, paracetamol use	1277/3927	2.10 (1.79–2.48)	Table 2	Yes (only relevant estimate in study)
Droste et al ³² (2000) Overall analysis	0–1 y	Any	1–8 y	Ever-asthma at ages 7–8 y	No	None	55/1206	2.1 (1.3–3.7)	Table 1	No (crude association)
Overall analysis ^a	0–1 y	Any	1–8 y	Ever-asthma at ages 7–8 y	Yes (LRI)	Area, gender, parental asthma, parental hay fever, ≥ 2 older siblings, mom smoking in pregnancy, exposure to smoke in first 6 mo, LRI in infancy	53/1180	1.7 (1.0–3.1)	Table 2	Yes (this is the overall adjusted estimate of the study)
No parental hay fever	0–1 y	Any	1–8 y	Ever-asthma at ages 7–8 y	Yes (LRI)	Area, gender, parental asthma, >2 older siblings, mom smoking in pregnancy, exposure to smoke in first 6 mo, LRI in infancy	?/742	1.2 (0.5–2.9)	Table 3	No (this stratum was not of principal interest)
Parental hay fever	0–1 y	Any	1–8 y	Ever-asthma at ages 7–8 y	Yes (LRI)	Area, gender, parental asthma, >2 older siblings, mom smoking in pregnancy, exposure to smoke in first 6 mo, LRI in infancy	?/438	2.3 (1.1–5.1)	Table 3	No (this stratum was not of principal interest)
Floistrup et al ³³ (2006) Overall analysis ^a	0–1 y	Any	0–13 y	Ever-asthma at ages 5–13 y	No	Age, gender, country, mom smoking in pregnancy, mom asthma and/or rhinoconjunctivitis, dad asthma and/or rhinoconjunctivitis, older sibling, parental education, current smoking in house, house pets at ages 0–1 y, antipyretic use, measles, diet, measles-mumps-rubella vaccination	636/6630	2.79 (2.03–3.83)	Table 3	Yes (only relevant adjusted estimate in study)
Foliaki et al ³⁴ (2009) Children with full covariate data; full model ^a	0–1 y	Any	0–7 y	Ever-asthma at ages 6–7 y	No	Gender, region, language, gross national income, mom education, breastfeeding, current mom smoking, current dad smoking, vegetable diet, pulses diet, fruit diet, paracetamol use in first year, paracetamol use currently, older siblings, younger siblings	?/103 653	1.94 (1.83–2.06)	Table 1	Yes (most adjusted estimate)

Stratum Type	Age at Antibiotic Use	No. of Courses	Age at First Symptoms or Diagnosis	Type of Outcome	Adjusted for Respiratory Infection?	Covariates	No. of Cases/Total	Estimate (95% CI)	Location of Estimate in Article	Used in Meta-analysis? (Rationale)
Children with full covariate data; minimal adjustment	0–1 y	Any	0–7 y	Ever-asthma at ages 6–7 y	No	Gender, region, language, gross national income	?/103 653	2.21 (2.08–2.34)	Table 1	No (estimate not fully adjusted)
All children; minimal adjustment	0–1 y	Any	0–7 y	Ever-asthma at ages 6–7 y	No	Gender, region, language, gross national income	?/193 412	2.13 (2.04–2.23)	Table 1	No (estimate not fully adjusted)
Karimi et al ⁵⁵ (2009)	Ages 0–1 y	Any	0–7 y	Ever-asthma at ages 6–7 y	No	None	49/1455	2.21 (1.05–4.80)	Table 1	Yes (only relevant estimate in study)
Overall analysis ^a										
Kozynskij et al ⁵⁶ (2007)	0–1 y	1–2	1–7 y	Current asthma at age 7 y	Yes	LRI, non-respiratory tract infections, mom asthma, No. of health care visits in first year, No. of siblings, urban location, gender	787/13 116	1.21 (1.01–1.46)	Table 2	Yes (full model adjusted for LRI and non-respiratory infections; collapsed for any-use analysis, and used for dose-response analysis)
According to dose; final model ^a	0–1 y	3–4	1–7 y	Current asthma at age 7 y	Yes	LRI, non-respiratory tract infections, mom asthma, No. of health care visits in first year, No. of siblings, urban location, gender	787/13 116	1.30 (1.04–1.53)	Table 2	Yes (see above)
According to dose; final model ^a	0–1 y	>4	1–7 y	Current asthma at age 7 y	Yes	LRI, non-respiratory tract infections, mom asthma, No. of health care visits in first year, No. of siblings, urban location, gender	787/13 116	1.46 (1.14–1.88)	Table 2	Yes (see above)
According to dose; adjusted for LRI	0–1 y	1–2	1–7 y	Current asthma at age 7 y	Yes	Gender, location, mom history of asthma, No. of health care visits, No. of siblings, LRI	787/13 116	1.25 (1.04–1.51)	Table 1	No (not full model)
According to dose; adjusted for LRI	0–1 y	3–4	1–7 y	Current asthma at age 7 y	Yes	Gender, location, mom history of asthma, No. of health care visits, No. of siblings, LRI	787/13 116	1.36 (1.08–1.70)	Table 1	No (not full model)
According to dose; adjusted for LRI	0–1 y	>4	1–7 y	Current asthma at age 7 y	Yes	Gender, location, mom history of asthma, No. of health care visits, No. of siblings, LRI	787/13 116	1.64 (1.29–2.10)	Table 1	No (not full model)
According to dose; adjusted for URI	0–1 y	1–2	1–7 y	Current asthma at age 7 y	Yes	Gender, location, mom history of asthma, No. of health care visits, No. of siblings, URI	787/13 116	1.27 (1.05–1.53)	Table 1	No (not full model)
According to dose; adjusted for URI	0–1 y	3–4	1–7 y	Current asthma at age 7 y	Yes	Gender, location, mom history of asthma, No. of health care visits, No. of siblings, URI	787/13 116	1.40 (1.10–1.78)	Table 1	No (not full model)
According to dose; adjusted for URI	0–1 y	>4	1–7 y	Current asthma at age 7 y	Yes	Gender, location, mom history of asthma, No. of health care visits, No. of siblings, URI	787/13 116	1.72 (1.27–2.34)	Table 1	No (not full model)

SUPPLEMENTAL TABLE 5 Continued

Stratum Type	Age at Antibiotic Use	No. of Courses	Age at First Symptoms or Diagnosis	Type of Outcome	Adjusted for Respiratory Infection?	Covariates	No. of Cases/Total	Estimate (95% CI)	Location of Estimate in Article	Used in Meta-analysis? (Rationale)
According to dose; adjusted for non-respiratory tract infections	0–1 y	1–2	1–7 y	Current asthma at age 7 y	No	Gender, location, mom history of asthma, No. of health care visits, No. of siblings, non-respiratory infections	787/13 116	1.23 (1.02–1.48)	Table 1	No (not full model)
According to dose; adjusted for non-respiratory tract infections	0–1 y	3–4	1–7 y	Current asthma at age 7 y	No	Gender, location, mom history of asthma, No. of health care visits, No. of siblings, non-respiratory infections	787/13 116	1.35 (1.07–1.69)	Table 1	No (not full model)
According to dose; adjusted for non-respiratory tract infections	0–1 y	>4	1–7 y	Current asthma at age 7 y	No	Gender, location, mom history of asthma, No. of health care visits, No. of siblings, non-respiratory infections	787/13 116	1.56 (1.22–2.00)	Table 1	No (not full model)
According to indication: antibiotics for nonrespiratory infection vs none	0–1 y	Any	1–7 y	Current Asthma at age 7 y	No	Mom history of asthma, No. of health care visits in first year, No. of siblings, household income, urban location, gender	? (n = 148 exposed)	1.86 (1.02–3.37)	Results, para 4	No (small number with exposure)
Estimates were also stratified according to urban area, rural area, maternal asthma, no maternal asthma, dog exposure, and no dog exposure, but are not listed here	—	—	—	—	—	—	—	—	Table 3	No (strata are not of principal interest)
Kusel et al ³⁷ (2008)										
Current asthma and according to time of exposure, 0–12 mo ^a	0–12 mo	Any	0–5 y	Current asthma at ages 4–5 y	No	Antibiotic predictor score, gender, any first-year pets, child-care, general practitioner visits	37/198	0.90 (0.4–2.3)	Table 3	Yes (for any exposure analysis; estimate is for current asthma and encompasses a full-year exposure period)
Current asthma and according to time of exposure, 0–6 mo	0–6 mo	Any	0–5 y	Current asthma at ages 4–5 y	No	Antibiotic predictor score, gender, any first-year pets, child-care, general practitioner visits	37/198	1.4 (0.6–3.2)	Table 3	No (estimate only encompasses a 6-mo exposure period)
Ever doctor-diagnosed asthma and according to time of exposure, 0–12 mo	0–12 mo	Any	0–5 y	Ever-asthma at ages 4–5 y	No	Antibiotic predictor score, gender, any first-year pets, child-care, general practitioner visits	57/198	1.5 (0.7–3.2)	Table 3	No (estimate is for ever-asthma)
Ever doctor-diagnosed asthma and according to time of exposure, 0–6 mo	0–6 mo	Any	0–5 y	Ever-asthma at ages 4–5 y	No	Antibiotic predictor score, gender, any first-year pets, child-care, general practitioner visits	57/198	1.7 (0.8–3.6)	Table 3	No (estimate is for ever-asthma)

Stratum Type	Age at Antibiotic Use	No. of Courses	Age at First Symptoms or Diagnosis	Type of Outcome	Adjusted for Respiratory Infection?	Covariates	No. of Cases/Total	Estimate (95% CI)	Location of Estimate in Article	Used in Meta-analysis? (Rationale)
Current atopic asthma and according to time of exposure, 0–12 mo	0–12 mo	Any	0–5 y	Current atopic asthma at ages 4–5 y	No	Antibiotic predictor score, gender, any first-year pets, child-care, general practitioner visits	28/198	1.1 (0.4–3.1)	Table 3	No (estimate is for a particular asthma phenotype; case number is smaller than that for any asthma)
Current atopic asthma and according to time of exposure, 0–6 mo	0–6 mo	Any	0–5 y	Current atopic asthma at ages 4–5 y	No	Antibiotic predictor score, gender, any first-year pets, child care, general practitioner visits	28/198	1.4 (0.5–3.4)	Table 3	No (estimate is for a particular asthma phenotype; case number is smaller than that for any asthma)
Current asthma and according to time of exposure, 0–12 mo ^a	0–12 mo	1	0–5 y	Current asthma at ages 4–5 y	No	Antibiotic predictor score, gender, any first-year pets, child care, general practitioner visits	37/198	1.22 (0.48–3.11)	Fig 1	Yes (for dose-responses analysis; estimates are approximated by inspection of the figure)
Current asthma and according to time of exposure, 0–12 mo ^a	0–12 mo	2	0–5 y	Current asthma at ages 4–5 y	No	Antibiotic predictor score, gender, any first-year pets, child care, general practitioner visits	37/198	0.51 (0.14–1.87)	Fig 1	Yes (for dose-responses analysis; estimates are approximated by inspection of the figure)
Current asthma and according to time of exposure, 0–12 mo ^a	0–12 mo	≥3	0–5 y	Current asthma at ages 4–5 y	No	Antibiotic predictor score, gender, any first-year pets, child care, general practitioner visits	37/198	0.51 (0.08–3.11)	Fig 1	Yes (for dose-responses analysis; estimates are approximated by inspection of the figure)
Dose-response estimates also provided for doctor-diagnosed asthma but are not listed here	—	—	—	—	—	—	—	—	Fig 1	No (these estimates are for ever-asthma)
Mai et al. ³⁸ (2010) Excluding symptoms with wheeze, asthma, or eczema in first YOI ^a	0–1 y	Any	1–4 y	Current asthma at age 4 y	Yes	Pneumonia, bronchitis, otitis, gender, young mom age, older sibling, mom smoking, parental allergy (history of asthma and/or hay fever), exclusive breastfeeding	?/2424	1.2 (0.8–1.7)	Results para 6	Yes (for any exposure analysis; estimate excludes asthma symptoms in ages 0–1 y)
Overall analysis at age 4 y	0–1 y	Any	0–4 y	Current asthma at age 4 y	No	Gender, young mom age, older sibling, mom smoking, parental allergy, exclusive breastfeeding	228/3306	1.5 (1.1–2.0)	Table 2	No (estimate does not exclude symptoms in ages 0–1 y)
Overall analysis at age 4 y, adjusted for respiratory infections	0–1 y	Any	0–4 y	Current asthma at age 4 y	Yes	Pneumonia, bronchitis, otitis, gender, young mom age, older sibling, mom smoking, parental allergy (history of asthma and/or hay fever), exclusive breastfeeding	228/3306	1.4 (1.1–1.7)	Table 3	No (estimate does not exclude symptoms in ages 0–1 y)
Overall analysis at age 8 y	0–1 y	Any	0–8 y	Current asthma at age 8 y	No	Gender, young mom age, older sibling, mom smoking, parental allergy, exclusive breastfeeding	210/3306	1.2 (0.9–1.6)	Table 4	No (estimate does not exclude symptoms in ages 0–1 y)

SUPPLEMENTAL TABLE 5 Continued

Stratum Type	Age at Antibiotic Use	No. of Courses	Age at First Symptoms or Diagnosis	Type of Outcome	Adjusted for Respiratory Infection?	Covariates	No. of Cases/Total	Estimate (95% CI)	Location of Estimate in Article	Used in Meta-analysis? (Rationale)
Overall analysis at age 8 y, adjusted for respiratory infections	0–1 y	Any	0–8 y	Current asthma at age 8 y	Yes	Pneumonia, bronchitis, otitis, gender, young mom age, older sibling, mom smoking, parental allergy (history of asthma and/or hay fever), exclusive breastfeeding	210/3306	1.2 (0.9–1.5)	Table 5	No (estimate does not exclude symptoms in ages 0–1 y)
According to dose at age 4 y ^a	0–1 y	1	0–4 y	Current asthma at age 4 y	Yes	Pneumonia, bronchitis, otitis, gender, young mom age, older sibling, mom smoking, parental allergy (history of asthma and/or hay fever), exclusive breastfeeding	228/3306	1.1 (0.7–1.6)	Table 6	Yes (used for dose-response analysis; age at outcome is closest to that of principal interest)
According to dose at age 4 y ^a	0–1 y	>1	0–4 y	Current asthma at age 4 y	Yes	Pneumonia, bronchitis, otitis, gender, young mom age, older sibling, mom smoking, parental allergy (history of asthma and/or hay fever), exclusive breastfeeding	228/3306	1.9 (1.2–3.0)	Table 6	Yes (used for dose-response analysis; age at outcome is closest to that of principal interest)
According to dose at age 8 y	0–1 y	1	0–8 y	Current asthma at age 8 y	Yes	Pneumonia, bronchitis, otitis, gender, young mom age, older sibling, mom smoking, parental allergy (history of asthma and/or hay fever), exclusive breastfeeding	210/3306	1.1 (0.7–1.6)	Table 6	No (age at outcome is of less interest than that for the estimate at age 4 y)
According to dose at age 8 y	0–1 y	>1	0–8 y	Current asthma at age 8 y	Yes	Pneumonia, bronchitis, otitis, gender, young mom age, older sibling, mom smoking, parental allergy (history of asthma and/or hay fever), exclusive breastfeeding	210/3306	1.5 (0.9–2.4)	Table 6	No (age at outcome is of less interest than that for the estimate at age 4 y)
According to dose at age 4 y, excluding children with wheeze, asthma, or eczema in first year	0–1 y	>1	1–4 y	Current asthma at age 4 y	Yes	Pneumonia, bronchitis, otitis, gender, young mom age, older sibling, mom smoking, parental allergy (history of asthma and/or hay fever), exclusive breastfeeding	?/2424	1.3 (0.6–2.9)	Results para 7	No (estimate for 1 course only not provided)
Marra et al ³⁸ (2009) Overall analysis ^a	0–1 y	Any	2–9 y	Incident asthma at ages 2–9 y	Yes	Gender, area, socioeconomic status, birth weight, gestational age, delivery method, No. of physician visits, allergist/respirologist/immunologist visit, surgery, congenital anomalies, No. of otitis media diagnoses, No. of bronchitis diagnoses, No. of URI diagnoses, No. of LRI diagnoses	18 864/251 817	1.12 (1.08–1.16)	Table 3 and 4	Yes (for any exposure analysis)
According to age at diagnosis	0–1 y	Any	2–3 y	Incident asthma at ages 2–3 y	Yes	Gender, area, socioeconomic status, birth weight, gestational age, delivery method, No. of physician visits, allergist/respirologist/immunologist visit, surgery, congenital anomalies, No. of otitis media diagnoses, No. of bronchitis diagnoses, No. of URI diagnoses, No. of LRI diagnoses	6239/251 817	1.12 (1.08–1.16)	Table 3	No (estimate is same as that above, assuming proportional hazards across ages)

SUPPLEMENTAL TABLE 5 Continued

Stratum Type	Age at Antibiotic Use	No. of Courses	Age at First Symptoms or Diagnosis	Type of Outcome	Adjusted for Respiratory Infection?	Covariates	No. of Cases/Total	Estimate (95% CI)	Location of Estimate in Article	Used in Meta-analysis? (Rationale)
According to age at diagnosis	0–1 y	Any	3–5 y	Incident asthma at ages 3–5 y	Yes	Gender, area, socioeconomic status, birth weight, gestational age, delivery method, No. of physician visits, allergist/respirologist/immunologist visit, surgery, congenital anomalies, No. of otitis media diagnoses, No. of bronchitis diagnoses, No. of URI diagnoses, No. of LRI diagnoses	8133/251 817	1.12 (1.08–1.16)	Table 3	No (estimate is same as that above, assuming proportional hazards across ages)
According to age at diagnosis	0–1 y	Any	5–9 y	Incident asthma at ages 5–9 y	Yes	Gender, area, socioeconomic status, birth weight, gestational age, delivery method, No. of physician visits, allergist/respirologist/immunologist visit, surgery, congenital anomalies, No. of otitis media diagnoses, No. of bronchitis diagnoses, No. of URI diagnoses, No. of LRI diagnoses	4492/25 1817	1.12 (1.08–1.16)	Table 3	No (estimate is same as that above, assuming proportional hazards across ages)
According to No. of courses ^a	0–1 y	1–2	2–9 y	Incident asthma at ages 2–9 y	Yes	Gender, area, socioeconomic status, birth weight, gestational age, delivery method, No. of physician visits, allergist/respirologist/immunologist visit, surgery, congenital anomalies, No. of otitis media diagnoses, No. of bronchitis diagnoses, No. of URI diagnoses, No. of LRI diagnoses	?/226 400	1.11 (1.07–1.15)	Table 4	Yes (for dose response)
According to No. of courses ^a	0–1 y	3–4	2–9 y	Incident asthma at ages 2–9 y	Yes	Gender, area, socioeconomic status, birth weight, gestational age, delivery method, No. of physician visits, allergist/respirologist/immunologist visit, surgery, congenital anomalies, No. of otitis media diagnoses, No. of bronchitis diagnoses, No. of URI diagnoses, No. of LRI diagnoses	?/161 354	1.15 (1.09–1.22)	Table 4	Yes (for dose response)

SUPPLEMENTAL TABLE 5 Continued

Stratum Type	Age at Antibiotic Use	No. of Courses	Age at First Symptoms or Diagnosis	Type of Outcome	Adjusted for Respiratory Infection?	Covariates	No. of Cases/Total	Estimate (95% CI)	Location of Estimate in Article	Used in Meta-analysis? (Rationale)
According to No. of courses ^a	0–1 y	>4	2–9 y	Incident asthma at ages 2–9 y	Yes	Gender, area, socioeconomic status, birth weight, gestational age, delivery method, No. of physician visits, allergist/respirologist/immunologist visit, surgery, congenital anomalies, No. of otitis media diagnoses, No. of bronchitis diagnoses, No. of URI diagnoses, No. of LRI diagnoses	?/149 875	1.30 (1.20–1.41)	Table 4	Yes (for dose response)
According to type, amoxicillin ^a	0–1 y	Any	2–9 y	Incident asthma at ages 2–9 y	Yes	Gender, area, socioeconomic status, birth weight, gestational age, delivery method, No. of physician visits, allergist/respirologist/immunologist visit, surgery, congenital anomalies, No. of otitis media diagnoses, No. of bronchitis diagnoses, No. of URI diagnoses, No. of LRI diagnoses	?/227 781	1.05 (1.02–1.09)	Table 4	Yes (for analysis according to type)
According to type, penicillin ^a	0–1 y	Any	2–9 y	Incident asthma at ages 2–9 y	Yes	Gender, area, socioeconomic status, birth weight, gestational age, delivery method, No. of physician visits, allergist/respirologist/immunologist visit, surgery, congenital anomalies, No. of otitis media diagnoses, No. of bronchitis diagnoses, No. of URI diagnoses, No. of LRI diagnoses	?/149 347	1.10 (1.02–1.19)	Table 4	Yes (for analysis according to type)
According to type, cephalosporin ^a	0–1 y	Any	2–9 y	Incident asthma at ages 2–9 y	Yes	Gender, area, socioeconomic status, birth weight, gestational age, delivery method, No. of physician visits, allergist/respirologist/immunologist visit, surgery, congenital anomalies, No. of otitis media diagnoses, No. of bronchitis diagnoses, No. of URI diagnoses, No. of LRI diagnoses	?/163 590	1.08 (1.03–1.13)	Table 4	Yes (for analysis according to type)
According to type, sulfonamide ^a	0–1 y	Any	2–9 y	Incident asthma at ages 2–9 y	Yes	Gender, area, socioeconomic status, birth weight, gestational age, delivery method, No. of physician visits, allergist/respirologist/immunologist visit, surgery, congenital anomalies, No. of otitis media diagnoses, No. of bronchitis diagnoses, No. of URI diagnoses, No. of LRI diagnoses	?/162 900	1.03 (0.98–1.08)	Table 4	Yes (for analysis according to type)

SUPPLEMENTAL TABLE 5 Continued

Stratum Type	Age at Antibiotic Use	No. of Courses	Age at First Symptoms or Diagnosis	Type of Outcome	Adjusted for Respiratory Infection?	Covariates	No. of Cases/Total	Estimate (95% CI)	Location of Estimate in Article	Used in Meta-analysis? (Rationale)
According to type, macrolide ^a	0–1 y	Any	2–9 y	Incident asthma at ages 2–9 y	Yes	Gender, area, socioeconomic status, birth weight, gestational age, delivery method, No. of physician visits, allergist/respirologist/immunologist visit, surgery, congenital anomalies, No. of otitis media diagnoses, No. of bronchitis diagnoses, No. of URI diagnoses, No. of LRI diagnoses	?/166 157	1.11 (1.06–1.17)	Table 4	Yes (for analysis according to type)
According to type, other ^a	0–1 y	Any	2–9 y	Incident asthma at ages 2–9 y	Yes	Gender, area, socioeconomic status, birth weight, gestational age, delivery method, No. of physician visits, allergist/respirologist/immunologist visit, surgery, congenital anomalies, No. of otitis media diagnoses, No. of bronchitis diagnoses, No. of URI diagnoses, No. of LRI diagnoses	?/143 209	0.93 (0.69–1.26)	Table 4	Yes (for analysis according to type)
Antibiotics not dispensed for respiratory infection or otitis media	0–1 y	Any	2–9 y	Incident asthma at ages 2–9 y	Yes	Gender, area, socioeconomic status, birth weight, gestational age, delivery method, No. of physician visits, allergist/respirologist/immunologist visit, surgery, congenital anomalies, No. of otitis media diagnoses, No. of bronchitis diagnoses, No. of URI diagnoses, No. of LRI diagnoses	18 864/251 817	1.13 (1.09–1.16)	Table 5	No (reduced number exposed; estimate is similar to that of full cohort)
Excluding children with respiratory infection or otitis media in first YOL	0–1 y	Any	2–9 y	Incident asthma at ages 2–9 y	Yes	Gender, area, socioeconomic status, birth weight, gestational age, delivery method, No. of physician visits, allergist/respirologist/immunologist visit, surgery, congenital anomalies, No. of otitis media diagnoses, No. of bronchitis diagnoses, No. of URI diagnoses, No. of LRI diagnoses	?/102 789	1.17 (1.10–1.25)	Table 5	No (not full cohort)
According to age at diagnosis, without proportional hazard	0–1 y	Any	2–3 y	Incident asthma at ages 2–3 y	Yes	Gender, area, socioeconomic status, birth weight, gestational age, delivery method, No. of physician visits, allergist/respirologist/immunologist visit, surgery, congenital anomalies, No. of otitis media diagnoses, No. of bronchitis diagnoses, No. of URI diagnoses, No. of LRI diagnoses	6239/251 817	1.16 (1.10–1.23)	By correspondence with authors	No (not overall analysis)

SUPPLEMENTAL TABLE 5 Continued

Stratum Type	Age at Antibiotic Use	No. of Courses	Age at First Symptoms or Diagnosis	Type of Outcome	Adjusted for Respiratory Infection?	Covariates	No. of Cases/Total	Estimate (95% CI)	Location of Estimate in Article	Used in Meta-analysis? (Rationale)
According to age at diagnosis, without proportional hazard	0–1 y	Any	3–5 y	Incident asthma at ages 3–5 y	Yes	Gender, area, socioeconomic status, birth weight, gestational age, delivery method, No. of physician visits, allergist/respirologist/immunologist visit, surgery, congenital anomalies, No. of otitis media diagnoses, No. of bronchitis diagnoses, No. of URI diagnoses, No. of LRI diagnoses	8133/251 817	1.10 (1.05–1.16)	By correspondence with authors	No (not overall analysis)
According to age at diagnosis, without proportional hazard	0–1 y	Any	5–9 y	Incident asthma at ages 5–9 y	Yes	Gender, area, socioeconomic status, birth weight, gestational age, delivery method, No. of physician visits, allergist/respirologist/immunologist visit, surgery, congenital anomalies, No. of otitis media diagnoses, No. of bronchitis diagnoses, No. of URI diagnoses, No. of LRI diagnoses	4492/251 817	1.10 (1.03–1.18)	By correspondence with authors	No (not overall analysis)
Martel et al ⁴⁰ (2009) Full cohort ^a	0–6 mo	Any	0–10 y	Incident asthma at ages 0–10 y	No	Gender, small for gestational age, allergic rhinitis, atopic dermatitis, mom age, mom receipt of welfare, mom education, area, No. of prenatal visits, obstetrician visits, mode of delivery, pregnancy in previous year, use of intranasal corticosteroids, antibiotics in pregnancy, asthma in pregnancy, mom chronic hypertension, pregnancy-induced hypertension, mom diabetes mellitus, mom gestational diabetes	5226/109 746	1.59 (1.50–1.68)	Table 1	Yes (used for full cohort analysis)
Nested case control; age-at-diagnosis stratum 3–10 y ^a	0–6 mo	Any	3–10 y	Incident asthma at ages 3–10 y	No	Allergic rhinitis, atopic dermatitis, mom asthma in pregnancy, mom chronic hypertension	935/19 635	1.29 (1.12–1.49)	Table 4	Yes (used for subcohort analysis; most suitable estimate according to age at diagnosis)
Nested case control; age-at-diagnosis stratum 0–2 y	0–6 mo	Any	0–2 y	Incident asthma at ages 0–2 y	No	Gender, allergic rhinitis, atopic dermatitis, mom age, mom receipt of welfare, mom education, No. of prenatal visits, mode of delivery, antibiotics in pregnancy, asthma in pregnancy, mom hypertension	4291/90 111	1.66 (1.55–1.77)	Table 4	No (low age at incidence)
Nested case control; final multivariate analysis	0–6 mo	Any	0–10 y	Incident asthma at ages 0–10 y	Yes	Gender, atopic dermatitis, oxygen use while newborn, bronchopulmonary disease, breastfeeding, mom receipt of welfare, asthma in pregnancy, mom use of intranasal corticosteroids in pregnancy, antibiotics in pregnancy, dad asthma, sibling asthma, fireplace in home, day-care use, pets in home	745/1578	1.70 (1.34–2.15)	Table 3	No (small sample size)

Stratum Type	Age at Antibiotic Use	No. of Courses	Age at First Symptoms or Diagnosis	Type of Outcome	Adjusted for Respiratory Infection?	Covariates	No. of Cases/Total	Estimate (95% CI)	Location of Estimate in Article	Used in Meta-analysis? (Rationale)
McKeever et al ⁴¹ (2002)										
Antibiotic type: penicillin	0–1 y	Any	1–9 y	Incident asthma at ages 1–9 y	No	Consultations in first YOL	2948/21 129	0.99 (0.89–1.10)	Table 2	Yes (for analysis according to type)
Antibiotic type: amoxicillin	0–1 y	Any	1–9 y	Incident asthma at ages 1–9 y	No	Consultations in first YOL	2948/21 129	1.25 (1.16–1.36)	Table 2	Yes (for analysis according to type)
Antibiotic type: macrolides	0–1 y	Any	1–9 y	Incident asthma at ages 1–9 y	No	Consultations in first YOL	2948/21 129	1.41 (1.30–1.53)	Table 2	Yes (for analysis according to type)
Antibiotic type: cephalosporins	0–1 y	Any	1–9 y	Incident asthma at ages 1–9 y	No	Consultations in first YOL	2948/21 129	1.44 (1.28–1.63)	Table 2	Yes (for analysis according to type)
Antibiotic type: augmentin	0–1 y	Any	1–9 y	Incident asthma at ages 1–9 y	No	Consultations in first YOL	2948/21 129	1.43 (1.19–1.72)	Table 2	Yes (for analysis according to type)
According to No. of courses ^a	0–1 y	1	1–9 y	Incident asthma at ages 1–9 y	No	Consultations in first YOL	?/13,171	1.26 (1.13–1.40)	Table 2	Yes (collapsed for any-use analysis; also used for dose-response analysis)
According to No. of courses ^a	0–1 y	2	1–9 y	Incident asthma at ages 1–9 y	No	Consultations in first YOL	?/11 078	1.46 (1.30–1.65)	Table 2	Yes (collapsed for any-use analysis; also used for dose-response analysis)
According to No. of courses ^a	0–1 y	3	1–9 y	Incident asthma at ages 1–9 y	No	Consultations in first YOL	?/9675	1.76 (1.56–2.01)	Table 2	Yes (collapsed for any-use analysis; also used for dose-response analysis)
According to No. of courses ^a	0–1 y	4	1–9 y	Incident asthma at ages 1–9 y	No	Consultations in first YOL	?/8811	1.82 (1.56–2.13)	Table 2	Yes (collapsed for any-use analysis; also used for dose-response analysis)
According to No. of courses ^a	0–1 y	>4	1–9 y	Incident asthma at ages 1–9 y	No	Consultations in first YOL	?/8922	1.99 (1.72–2.31)	Table 2	Yes (collapsed for any-use analysis; also used for dose-response analysis)
Ponsonby et al ⁴² (1999)										
Full model ^a	0–5 or 0–40 wk	Any	0–7 y	Ever-asthma at age 7 y	No	Family history of asthma, exclusive breastfeeding, mom postnatal smoking, other house smoking, low birth weight, prematurity, gas heater, No. of residents in house, postnatal age at interview	276/856	1.04 (0.78–1.37)	Table 2	Yes (most adjusted estimate in study)
Only adjusted for family history	0–5 or 0–40 wk	Any	0–7 y	Ever-asthma at age 7 y	No	Family history of asthma	276/856	1.04 (0.80–1.36)	Table 2	No (estimate not fully adjusted)
Sobko et al ⁴³ (2010)										
Overall analysis ^a	Neonatal period	At least 4 doses	0–23 y	Ever-asthma at ages 7–23 y	No	Analysis group, birth weight, gestational age, mom's education, gender, No. of older siblings, year of birth	40/201	1.48 (0.93–2.35)	Table 2	Yes (only relevant estimate in study)

SUPPLEMENTAL TABLE 5 Continued

Stratum Type	Age at Antibiotic Use	No. of Courses	Age at First Symptoms or Diagnosis	Type of Outcome	Adjusted for Respiratory Infection?	Covariates	No. of Cases/Total	Estimate (95% CI)	Location of Estimate in Article	Used in Meta-analysis? (Rationale)
Su et al ⁴⁴ (2010)	According to age at outcome	0–9 mo	Any	0–3 y	Current asthma at age 3 y	No	None	1.68 (0.75–3.79)	Table 3	No (smaller case number for current asthma)
	According to age at outcome ^a	0–9 mo	Any	0–5 y	Current asthma at age 5 y	No	None	1.87 (0.95–3.67)	Table 3	Yes (for any exposure analysis; largest case number for current asthma)
	According to age at outcome	0–9 mo	Any	0–5 y	Ever-asthma at age 5 y	No	None	1.79 (0.98–3.27)	Table 3	No (ever-asthma)
	According to No. of courses ^a	0–9 mo	1	0–5 y	Ever-asthma at age 5 y	No	None	1.45 (0.73–2.88) (Estimated from visual inspection of figure)	Fig 1	Yes (for dose-response analysis)
Wickens et al ⁴⁶ (1999)	According to No. of courses ^a	0–9 mo	≥2	0–5 y	Ever-asthma at age 5 y	No	None	2.16 (0.87–5.36) (Estimated from visual inspection of figure)	Fig 1	Yes (for dose-response analysis)
	Overall analysis	0–1 y	Any	0–10 y	Ever-asthma at ages 5–10 y	No	Age, gender, ethnicity, family size, family history of asthma, eczema, hay fever, mom's smoking currently and in child's first YOL, dad's smoking currently and in child's first YOL	4.05 (1.55–10.59)	Table 3	No (asthma age is susceptible to protopathic bias)
	According to No. of courses ^a	0–1 y	1–2	0–10 y	Ever-asthma at ages 5–10 y	No	Age, gender, ethnicity, family size, family history of asthma, eczema, hay fever, mom's smoking currently and in child's first YOL, dad's smoking currently and in child's first YOL	2.27 (1.14–4.51)	Table 3	Yes (used for dose response)
	According to No. of courses ^a	0–1 y	≥3	0–10 y	Ever-asthma at ages 5–10 y	No	Age, gender, ethnicity, family size, family history of asthma, eczema, hay fever, mom's smoking currently and in child's first YOL, dad's smoking currently and in child's first YOL	4.02 (1.57–10.31)	Table 3	Yes (used for dose response)
Age at first symptoms ^a	0–1 y	Any	1–10 y	Ever-asthma at ages 5–10 y	No	None	27/217	7.50 (2.56–22.00)	Table 4	Yes (for any exposure analysis; this stratum of outcome age least susceptible to protopathic bias)
Overall analysis	0–1 y	Any	1–4 y	Ever-asthma at ages 5–10 y	No	None	??	5.63 (1.81–17.45)	Results para 6	No (this stratum was not of principal interest)

Stratum Type	Age at Antibiotic Use	No. of Courses	Age at First Symptoms or Diagnosis	Type of Outcome	Adjusted for Respiratory Infection?	Covariates	No. of Cases/Total	Estimate (95% CI)	Location of Estimate in Article	Used in Meta-analysis? (Rationale)
Wickens et al ⁴⁵ (2008)										
Age at exposure and outcome; model ^a	0–15 mo	Any	1–4 y	Current asthma at ages 3–4 y	Yes	Chest infections at ages 0–4 y	2/847	0.98 (0.60–1.59)	Table 4	Yes (estimate adjusted for respiratory infections)
Age at exposure and outcome; model	0–15 mo	Any	1–4 y	Current asthma at ages 3–4 y	No	Gender, ethnicity, family history of eczema, hay fever, or asthma, parity, ear infection, antibiotic use between 15 mo and 4 y	2/847	0.78 (0.46–1.32)	Table 4	No (estimate not adjusted for respiratory infections)
Wjst et al ⁴⁷ (2001)										
Indication for antibiotics (pulmonary indications)	0–1 y	Any	0–14 y	Ever-asthma (any type) at ages 5–14 y	No	None	2/?	14.6 (4.2–51.0)	Results, para 6	No (this stratum was susceptible to protopathic bias)
Indication for antibiotics (nonpulmonary indications) ^a	0–1 y	Any	0–14 y	Ever-asthma (any type) at ages 5–14 y	No	None	2/?	2.4 (0.3–22.5)	Results, para 6	Yes (this stratum was least susceptible to protopathic bias, according to indication for antibiotic use)
Age at antibiotic exposure; outcome type	0–6 mo	Any	0–14 y	Ever-asthma (any type) at ages 5–14 y	No	Gender, season, community, age, parental education, family history of asthma	21/656	9.9 (3.1–31.4)	Table 5	No (this estimate was for any indication of antibiotic use)
Age at antibiotic exposure; outcome type	0–6 mo	Any	0–14 y	Ever-asthma (extrinsic) at ages 5–14 y	No	Gender, season, community, age, parental education, family history of asthma	15/656	7.1 (1.8–27.8)	Table 5	No (this estimate was for any indication of antibiotic use)
Age at antibiotic exposure; outcome type	0–6 mo	Any	0–14 y	Ever-asthma (intrinsic) at ages 5–14 y	No	Gender, season, community, age, parental education, family history of asthma	8/656	16.5 (1.9–147.2)	Table 5	No (this estimate was for any indication of antibiotic use)
Age at antibiotic exposure; outcome type	7–12 mo	Any	0–14 y	Ever-asthma (any type) at ages 5–14 y	No	Gender, season, community, age, parental education, family history of asthma	29/980	5.2 (1.7–15.6)	Table 5	No (this estimate was for any indication of antibiotic use)
Age at antibiotic exposure; outcome type	7–12 mo	Any	0–14 y	Ever-asthma (extrinsic) at ages 5–14 y	No	Gender, season, community, age, parental education, family history of asthma	19/980	3.5 (1.0–12.8)	Table 5	No (this estimate was for any indication of antibiotic use)
Age at antibiotic exposure; outcome type	7–12 mo	Any	0–14 y	Ever-asthma (intrinsic) at ages 5–14 y	No	Gender, season, community, age, parental education, family history of asthma	12/980	8.9 (1.1–74.5)	Table 5	No (this estimate was for any indication of antibiotic use)

Listed are all relevant estimates (ie, those that met review inclusion criteria) for each study of antibiotic use in the first year of life and childhood asthma. Other estimates may also be selected for dose-response analysis, as indicated. Crude estimates are not listed unless the study did not provide an adjusted estimate. Rationales are provided for the selection or nonselection of each estimate. Note that estimates for Celedón et al^{2a} (2004) were not used because of the early age of asthma outcome (ages 1–2 years). LRI indicates lower respiratory infection; URI, upper respiratory infection; YOL, year of life; ?, data not provided or unclear.

^a Only the estimate that was judged to be the least susceptible to protopathic bias (see "Methods") was selected for meta-analysis.

SUPPLEMENTAL TABLE 6 List of Eligible Study Estimates and Rationale for Use in the Meta-analysis

Stratum Type	Time of Antibiotic Use	No. of Courses	Age at First Symptoms or Diagnosis	Type of Outcome	Covariates	No. of Cases/Total	Estimate (95% CI)	Location of Estimate in Article	Used in Meta-analysis? (Rationale)
Benn et al ⁴⁸ (2002) Main analysis ^a	Any time in pregnancy	Any	0–5 y	Current asthma at ages 4–5 y	Low gestational age, maternal age, maternal education, maternal allergic disease	93/2742	1.7 (1.1–2.6)	Table 3	Yes (largest cohort size)
	Any time in pregnancy	Any	0–5 y	Current asthma at ages 4–5 y	Low gestational age, maternal age, maternal education, maternal allergic disease, breastfeeding	?/2098	1.8 (1.0–3.1)	Table 3	No; fewer cases
Martel et al ⁴⁰ (2009) Overall analysis ^a	Any time in pregnancy	Risk estimate is for each additional antibiotic prescription	0–10 y	Ever asthma ages 0–10 y	Child gender, small for gestational age, child allergic rhinitis, child atopic dermatitis, child antibiotics in first 6 mo, maternal age $\geq$ 35 y, maternal social welfare use, maternal education, rural living area, No. of prenatal visits, obstetrician visit during pregnancy, method of delivery, pregnancy in previous year, maternal use of intranasal corticosteroids, asthma during pregnancy, maternal chronic hypertension, pregnancy-induced hypertension, maternal diabetes mellitus, gestational diabetes	5226/109 746	1.09 (1.06–1.12)	Table 1	Yes (largest cohort size available)
	Any time in pregnancy	Risk estimate is for each additional antibiotic prescription	0–10 y	Ever asthma ages 0–10 y	Child gender, child atopic dermatitis, child antibiotics in first 6 mo, oxygen administration to newborn, child bronchopulmonary disease, breastfeeding, maternal social welfare use, asthma during pregnancy, maternal use of intranasal corticosteroids, parental asthma, sibling asthma, wood-burning fireplace in home, day-care attendance, pets in home	745/1568	1.15 (1.03–1.29)	Table 3	No (restricted cohort)
Stratified according to age of onset of asthma (child age $<$ 3 y)	Any time in pregnancy	Risk estimate is for each additional antibiotic prescription	0–2 y	Ever asthma ages 0–2 y	Child gender, child allergic rhinitis, child atopic dermatitis, child antibiotics in first 6 mo, maternal age $\geq$ 35 y, social welfare use, maternal education, No. of prenatal visits, mode of delivery, asthma during pregnancy, maternal hypertension	4291/90 111	1.10 (1.06–1.13)	Table 4	No (restricted cohort)

SUPPLEMENTAL TABLE 6 Continued

Stratum Type	Time of Antibiotic Use	No. of Courses	Age at First Symptoms or Diagnosis	Type of Outcome	Covariates	No. of Cases/Total	Estimate (95% CI)	Location of Estimate in Article	Used in Meta-analysis? (Rationale)
McKeever et al ⁴⁹ (2002)									
According to No. of courses, — main analysis	Any time in pregnancy	1	> Newborn	Ever asthma ages 0–10 y	Consulting behavior, maternal allergic disease	?/21 581 ^b	1.19 (1.09–1.31)	Table 2	No (not adjusted for infections)
	Any time in pregnancy	2	Newborn	Ever asthma ages 0–10 y	Consulting behavior, maternal allergic disease	?/17 924 ^b	1.31 (1.15–1.50)	Table 2	No (not adjusted for infections)
	Any time in pregnancy	>2	Newborn	Ever asthma ages 0–10 y	Consulting behavior, maternal allergic disease	?/17 213 ^b	1.63 (1.40–1.89)	Table 2	No (not adjusted for infections)
According to No. of courses, adjusted for No. of infections in pregnancy ^a	Any time in pregnancy	1	Newborn	Ever asthma ages 0–10 y	Consulting behavior, maternal allergic disease, No. of infections	?/21 581 ^b	1.15 (1.07–1.23)	Table 5	Yes (most completely adjusted model; collapsed for any exposure analysis)
According to No. of courses, adjusted for No. of infections in pregnancy ^a	Any time in pregnancy	2	Newborn	Ever asthma ages 0–10 y	Consulting behavior, maternal allergic disease, No. of infections	?/17 924 ^b	1.25 (1.13–1.39)	Table 5	Yes (most completely adjusted model; collapsed for any exposure analysis)
According to No. of courses, adjusted for No. of infections in pregnancy ^a	Any time in pregnancy	>2	Newborn	Ever asthma ages 0–10 y	Consulting behavior, maternal allergic disease, No. of infections	?/17 213 ^b	1.54 (1.36–1.74)	Table 5	Yes (most completely adjusted model; collapsed for any exposure analysis)

Listed are all relevant estimates (ie, those that met review inclusion criteria) for each study of antibiotic use during pregnancy and childhood asthma. Crude estimates are not listed here, unless the study did not provide an adjusted estimate. Rationales are provided for the selection or nonselection of each estimate. ? indicates data not provided or unclear.

^a Only the estimate that was judged to be the least susceptible to confounding while having the highest statistical power available was selected.

^b Total cohort: number of cases/total: 2671/24 690.

SUPPLEMENTAL TABLE 7 Sensitivity Analyses for Early-Life Exposure to Antibiotics and Risk of Childhood Asthma

Design	Prospective, All Asthma Incidence Ages (0–1 y)	Database			Prospective and Database, All Asthma Incidence Age (0–2 y)
		All Asthma Incidence Ages (0–2 y)	Asthma Incidence Ages 0–1 y ^a	Asthma Incidence Ages 2–3 y ^a	
All studies, OR (95% CI)	1.07 (0.89–1.28)	1.35 (1.12–1.62)	1.44 (1.21–1.72)	1.16 (1.06–1.25)	1.25 (1.08–1.45)
No. of studies and reference numbers	6 ^{30,37,38,42,44,45}	6 ^{29,36,39–41,43}	3 ^{36,41,43}	3 ^{29,39–40,b}	12 ^{29,30–36–45}
χ^2 , <i>P</i>	.45	<.0001	.10	.99	<.0001
<i>I</i> ² , %	0	96	56	0	92
	Prospective vs database (all ages) <i>P</i> .075	Database, age 0–1 vs 2 y, <i>P</i> .028			
Stratified according to asthma ascertainment method					
Doctor diagnosis, OR (95% CI)	1.08 (0.59–1.96)	1.33 (1.10–1.62)	1.44 (1.16–1.80)	1.16 (1.06–1.25)	1.29 (1.08–1.55)
No. of studies and reference number	3 ^{30,37,44}	5 ^{29,36,39–41}	2 ^{36,41}	3 ^{29,39,40,b}	8 ^{29,30,36,37,39–41,44}
χ^2 , <i>P</i>	.12	<.0001	.03	.99	<.0001
<i>I</i> ² , %	52	97	78	0	94
Doctor diagnosis, yes vs no, <i>P</i>	.98	.68	.92	NA	.32
No doctor diagnosis, OR (95% CI)	1.07 (0.88–1.31)	1.48 (0.93–2.35)	1.48 (0.93–2.35)	NA	1.13 (0.94–1.36)
No. of studies and reference number	3 ^{38,42,45}	1 ⁴³	1 ⁴³	0	4 ^{38,42,43,45}
χ^2 , <i>P</i>	.76	NA	NA	NA	.55
<i>I</i> ² , %	0	NA	NA	NA	0
Stratified according to adjustment or no adjustment for respiratory infections					
Adjusted for respiratory infections, OR (95% CI)	1.11 (0.83–1.49)	1.17 (1.06–1.29)	1.30 (1.15–1.47)	1.12 (1.08–1.16)	1.16 (1.08–1.25)
No. of studies and reference number	2 ^{38,45}	3 ^{29,36,39}	1 ³⁶	2 ^{29,39}	5 ^{29,36,38,39,45}
χ^2 , <i>P</i>	.51	.07	NA	.99	.22
<i>I</i> ² , %	0	62	NA	0	30
Adjusted for respiratory infections, yes vs no, <i>P</i>	.80	<.0001	.038	NA	.079
Not adjusted for respiratory infections, OR (95% CI)	1.05 (0.77–1.45)	1.59 (1.51–1.68)	1.61 (1.38–1.89)	1.29 (1.12–1.49)	1.38 (1.15–1.65)
No. of studies and reference number	4 ^{30,37,42,44}	3 ^{40,41,43}	2 ^{41,43}	1 ^{40,b}	7 ^{30,37,40–44}
χ^2 , <i>P</i>	.24	.92	.70	NA	.01
<i>I</i> ² , %	29	0	0	NA	64
Stratified according to adjustment or no adjustment for No. of medical consultations					
Adjusted for consultations, OR (95% CI)	0.90 (0.35–2.30)	1.32 (1.07–1.61)	1.44 (1.16–1.80)	1.12 (1.08–1.16)	1.30 (1.07–1.58)
No. of studies and reference number	1 ³⁷	3 ^{36,39,41}	2 ^{36,41}	1 ³⁹	4 ^{36,37,39,41}
χ^2 , <i>P</i>	NA	<.0001	.03	NA	<.0001
<i>I</i> ² , %	NA	91	78	NA	87
Adjusted for consultations, yes vs no, <i>P</i>	.71	.80	.92	.29	.66
Not adjusted for consultations, OR (95% CI)	1.08 (0.88–1.32)	1.38 (1.04–1.82)	1.48 (0.93–2.35)	1.21 (1.06–1.39)	1.22 (0.99–1.50)
No. of studies and reference number	5 ^{30,38,42,44,45}	3 ^{29,40,43}	1 ⁴³	2 ^{29,40,b}	8 ^{29,30,38,40,42–45}
χ^2 , <i>P</i>	.33	.0007	NA	.22	<.0001
<i>I</i> ² , %	13	86	NA	34	98
Stratified according to estimate type					
RR/HR estimate type, OR (95% CI)	1.04 (0.78–1.37)	1.42 (1.07–1.88)	1.63 (1.38–1.93)	1.18 (1.03–1.35)	1.33 (1.04–1.70)
No. of studies and reference number	1 ⁴²	3 ^{39–41}	1 ⁴¹	2 ^{39,40,b}	4 ^{39–42}
χ^2 , <i>P</i>	NA	<.0001	NA	.06	<.0001
<i>I</i> ² , %	NA	98	NA	71	98
RR/HR vs OR, <i>P</i>	.81	.38	.040	.64	.49
OR estimate type, OR (95% CI)	1.09 (0.84–1.42)	1.24 (1.10–1.40)	1.31 (1.16–1.48)	1.12 (0.94–1.33)	1.21 (1.08–1.35)
No. of studies and reference number	5 ^{30,37,38,44,45}	3 ^{29,36,43}	2 ^{36,43}	1 ²⁹	8 ^{29,30,36–38,43–45}
χ^2 , <i>P</i>	.32	.29	.60	NA	.32
<i>I</i> ² , %	14	19	0	NA	14

SUPPLEMENTAL TABLE 7 Continued

Design	Prospective, All Asthma Incidence Ages (0–1 y)	Database			Prospective and Database, All Asthma Incidence Age (0–2 y)
		All Asthma Incidence Ages (0–2 y)	Asthma Incidence Ages 0–1 y ^a	Asthma Incidence Ages 2–3 y ^a	
Stratified according to adjustment for family history of asthma					
Adjusted for family history of asthma ^c	1.09 (0.87–1.37)	1.45 (1.19–1.76)	1.30 (1.15–1.47)	1.29 (1.12–1.49)	1.32 (1.09–1.59)
No. of studies and reference number	2 ^{38,42}	2 ^{36,40}	1 ³⁶	1 ^{40,b}	4 ^{36,38,40,42}
χ^2 , <i>P</i>	.53	.003	NA	NA	.0005
<i>I</i> ² , %	0	88	NA	NA	83
Adjusted for family history, yes vs no, <i>P</i>	.62	.39	.038	.40	.82
No adjustment for family history of asthma ^c	1.29 (0.69–2.41)	1.28 (1.05–1.57)	1.61 (1.38–1.89)	1.21 (1.08–1.16)	1.28 (1.07–1.53)
No. of studies and reference number	2 ^{44,45}	4 ^{29,39,41,43}	2 ^{41,43}	2 ^{29,39}	6 ^{29,39,41,43–45}
χ^2 , <i>P</i>	.13	.0002	.70	.99	.0006
<i>I</i> ² , %	57	85	0	0	77
Cohorts with a family history of asthma	0.79 (0.48–1.28)	NA	NA	NA	0.79 (0.48–1.28)
No. of studies and reference number	2 ^{30,37}	0	0	0	2 ^{30,37}
χ^2 , <i>P</i>	.75	NA	NA	NA	.75
<i>I</i> ² , %	0	NA	NA	NA	0

NA indicates not applicable.

^a Martel et al⁴⁰ (2009) were included in the 2- to 3-year age group but not the 1- to 2-year age subgroup for database studies, using that study's age 3+ estimate.^b Indicates the use of the age 3+ estimate by Martel et al⁴⁰ (see the Martel et al entry, second row, in Supplemental Table 5).^c Not including data from Celedón et al³⁰ or Kusel et al³⁷ (studies with cohorts with a family history of asthma).