Does Antibiotic Exposure During Infancy Lead to Development of Asthma?*

A Systematic Review and Metaanalysis

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Objectives: **To determine the association between antibiotic exposure in the first year of life and the development of childhood asthma.**

Design: **Metaanalysis of observational studies retrieved through systematic search of all available electronic data sources. Studies included in the metaanalyses were those with populations exposed to one or more courses of antibiotics during the first year of life, and asthma diagnosis was defined as diagnosis by a physician between the age of 1 to 18 years.**

Setting: **Retrospective and prospective studies published in the English-language literature from 1966 to present.**

Results: **Eight studies (four prospective and four retrospective) examined the association between exposure to at least one course of antibiotics and development of childhood asthma. The total number of subjects for the analysis comparing exposure to at least one antibiotic to no exposure in the first year of life was 12,082 children and 1,817 asthma cases. In the dose-response analysis, we included data from a total of 27,167 children and 3,392 asthma cases. The pooled odds ratio (OR) for the eight studies was 2.05 (95% confidence interval [CI], 1.41 to 2.99). The association was significantly stronger in the retrospective studies (OR, 2.82; 95% CI, 2.07 to 3.85) than the prospective studies (OR, 1.12; 95% CI, 0.88 to 1.42). Five of the eight studies examined whether the association was related to the number of courses of antibiotics taken in the first year of life. The overall OR for the dose-response analysis was 1.16 (95% CI, 1.05 to 1.28) for each additional course of antibiotics; however, this association was not significantly stronger in the retrospective studies (OR, 1.37; 95% CI, 1.18 to 1.60) relative to the prospective studies (OR, 1.07; 95% CI, 0.95 to 1.20).**

Conclusions: **Exposure to at least one course of antibiotics in the first year of life appears to be a risk factor for the development of childhood asthma. Because of the limitations of the studies conducted to date, additional large-scale, prospective studies are needed to confirm this potential association.** ***(CHEST 2006; 129:610–618)***

Key words: antibiotics; childhood asthma; pediatrics

Abbreviations: CI = confidence interval; LRI = lower respiratory tract infection; OR = odds ratio

Antibiotics are commonly used to treat infections during early childhood. Increasing antibiotic use in children has been found to coincide with several factors, including an increase in the number of children in group child care,[1] an increase in physician visits for otitis media,[2] and a high rate of inappropriate prescribing for viral upper respiratory infections and bronchitis.[3] This increase in antibiotic use in children has been accompanied by an increase in the prevalence of asthma and has led to the hypothesis of a causal association. Asthma is now the most common chronic disease of childhood, with approximately one in eight school-aged children affected in western countries.[4,5] In industrialized countries, the prevalence of asthma has increased significantly over the last 30 years and is a major public health concern.[6–9] Although the reasons for the asthma epidemic are not clearly understood, one

hypothesis is that it is related to the exposure of infants to antibiotics. This postulate is consistent with the "hygiene hypothesis," which suggests that growing up in a more hygienic environment with less microbial exposure may increase atopic (T-helper type 2) immune responses and, thus, the development of asthma.[10,11] Although a number of studies have evaluated this association, the epidemiologic evidence is conflicting.

The objective of this study was to explore the association between exposure to antibiotics in the first year of life and the subsequent development of asthma. Specifically, we sought to evaluate the association between the receipt of a prescription for a course of antibiotics and the development of asthma, and to evaluate a potential dose-response relationship between the number of courses of antibiotics received and the development of asthma by conducting a metaanalysis.

Materials and Methods

Search Strategy

We systematically searched all available electronic databases, including MEDLINE, EMBASE, EBM databases (ACP, Central, CDSR, and DARE), Web of Science, PapersFirst, ProceedingsFirst, and the Cochrane database, for the period January 1966 to September 2004 for all English- and non–English-language articles using the medical subject headings *child*, *childhood*, *early life* or *early childhood* AND *asthma*, *atopic dermatitis*, *hay fever*, *allergic disease*, *allergy* or *atopy* AND *antibiotic*, *antimicrobial*, or *anti-bacterial*. All potentially relevant articles were then retrieved based on the consensus of two investigators, and their reference lists were searched for additional potentially relevant articles.

Data Extraction

Studies were included if they were published in English, explicitly defined *antibiotic exposure* as the receipt of at least one prescription for an antibiotic in the first year of life, and included the development of physician-diagnosed childhood asthma between the ages of 1 and 18 years as an outcome. Studies were excluded from the analysis if they did not investigate an association between antibiotic exposure and childhood asthma or did not report odds ratios (ORs) or relative risks with 95% confidence intervals (CI), or provide enough data to allow for their calculation. Study inclusion and exclusion was initially determined independently by two authors, and any discrepancies were resolved by consensus of all authors. Each study that met the inclusion criteria was then independently evaluated for methodologic quality based on a modified checklist developed by Downs and Black.[12] Evaluator's scores for all but one study differed by no more than 1 point; the evaluation of one study differed by 2 points. As expected, the quality scores for the prospective studies were higher than for the retrospective studies.

For studies that presented results for other allergic diseases such as atopy, hay fever, and eczema, only the risk estimates relevant to the asthma outcome were used. Additional data extracted included study design, number of patients in each study group, age range, gender, criteria for eligibility, covariates used to adjust the risk estimates and, when available, age of asthma diagnosis and the number of courses of antibiotics in the first year of life. Data were requested from the authors of included studies when it was not possible to determine the unadjusted OR for exposure to at least one antibiotic during the first year of life from the published data.

Data Analysis

Study-specific unadjusted ORs comparing at least one course of antibiotics taken vs no courses taken were weighted by the inverse of their variances to obtain a pooled OR with 95% CI. We evaluated whether a log-linear model could adequately describe the dose-response relationship between the number of antibiotic courses received and the risk of childhood asthma. The risk of asthma per course of antibiotic for each study and the pooled regression parameter were estimated using methods given by Berlin et al.[13] In order to assign a value to each category of courses of antibiotics taken, we used the midpoint between the boundaries of each exposure category. For open-ended categories, we assigned the value of 1.2 times the lower bound as suggested by Berlin et al.[13]

We calculated the Cochran Q statistic to test for statistical heterogeneity. Values of Q significantly > 0 ($p < 0.1$) were considered as evidence of heterogeneity. We elected to present the results of the random-effects models only, as we expected heterogeneity between studies. The analysis was restricted to subgroups according to the most important variables contributing to heterogeneity, and the effect of these variables on the study results was modeled via meta-regression. In addition, the plots of Galbraith[14] and L'Abbé et al[15] were used to examine possible sources of heterogeneity. Influence analyses were performed to assess whether any of the studies were overly influential in the metaanalysis. Finally, we visually inspected funnel plots to assess for potential publication bias.[16] Analyses were performed using statistical software (S-PLUS 6.2; Mathsoft; Seattle, WA; and SPSS 12.0; SPSS; Chicago, IL).

Results

Study Selection and Characteristics

Figure 1 summarizes the selection process for studies included in the metaanalysis. Our initial search identified 2,056 titles, of which 2,042 were excluded because they either did not investigate an association between antibiotic exposure and childhood asthma or were not in English. Of the 14 remaining articles, we excluded one study[17] that did

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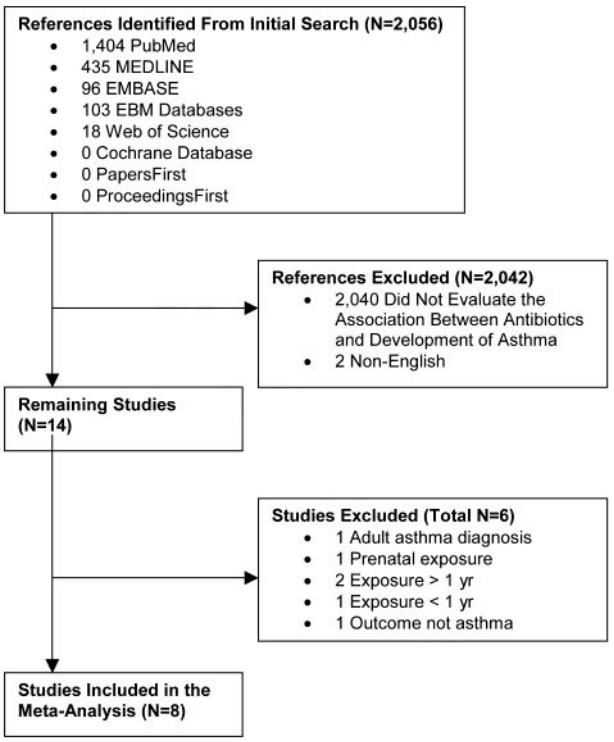

FIGURE 1. Flow diagram of study selection process.

not exclusively report childhood asthma diagnoses, one study[18] that only examined prenatal antibiotic exposure, three studies that investigated exposures at either < 1 year of age[19] or > 1 year of age,[20,21] and one study[22] in which a discrete diagnosis of asthma was not reported as an outcome. As such, eight articles[23–30] met our inclusion criteria (Table 1); half were prospective, and the other half were retrospective. The average scores on the criteria of Downs and Black[12] for these studies were lower for the retrospective studies (mean score, 14.6), compared to the prospective studies (mean score, 17.4). These studies were reported between 1999 and 2004 with sample sizes between 263 and 21,129 children. The published studies by Cohet et al,[24] Celedon et al,[25] McKeever et al,[26] and Illi et al[27] were supplemented by additional data from the authors. The article by Cohet et al[24] was a compilation of two studies using the same study design (retrospective cross-sectional survey) in different populations (childhood infection group and a general population group).

We included seven of the eight studies[23–25,27–30] in the analysis comparing exposure to at least one antibiotic to no exposure in the first year of life with a total of 12,082 children and 1,817 asthma cases. All included retrospective studies used questions from the International Study of Asthma and Allergies in Childhood survey. The study conducted by McKeever et al[26] was excluded from this analysis because the associated OR was not reported in the study and calculating a crude OR was not possible due to different follow-up times of patients. In the dose-response analysis, five studies[23,25,26,28,30] were included, reporting data from a total of 27,167 children and 3,392 asthma cases.

Analysis Associated With Exposure to at Least One Course of Antibiotic

Figure 2 summarizes the study specific and pooled ORs of asthma risk due to antibiotic exposure in the first year of life. The overall pooled OR was 2.05 (95% CI, 1.41 to 2.99). The association between antibiotic use in the first year of life and asthma was significantly stronger ($p = 0.02$) in the retrospective studies than in the prospective studies (Table 2). The pooled OR for the prospective studies was 1.12 (95% CI, 0.88 to 1.42), while the pooled OR for the retrospective studies was 2.82 (95% CI, 2.07 to 3.85). By visual inspection of the plots of Galbraith[14] and L'Abbé et al [15] (data not shown), the residual heterogeneity in the retrospective studies (Q statistic, 9.92; $p = 0.04$) was due to two studies[28,30] having significantly larger ($p = 0.005$) ORs than the others according to the meta-regression.

A subgroup analysis was performed for studies examining high-risk patients. Three of the eight studies[24,25,27] were conducted in high-risk populations, while the remainder were in the general population. The pooled OR for these studies was 1.38 (95% CI, 0.63 to 3.03), while the pooled OR for studies conducted in the general population (*ie*, not high risk) was 2.64 (95% CI, 1.56 to 4.45). Although the general population studies had a greater OR, this finding was not significant ($p = 0.30$).

Dose-Response Analysis

The overall OR for the dose-response association of antibiotic use in the first year of life and asthma was 1.16 (95% CI, 1.05 to 1.28), but there was a trend to a stronger association ($p = 0.08$) in the retrospective studies than in the prospective studies (Table 2). The pooled OR for the prospective studies was 1.07 (95% CI, 0.95 to 1.20), while the pooled OR for the retrospective studies was 1.37 (95% CI, 1.18 to 1.60). Heterogeneity was still suspected within the prospective studies (Q statistic, 24.15; $p < 0.001$), but not within the retrospective studies (Q statistic, 1.48; $p = 0.22$). The plots of Galbraith[14] and L'Abbé et al[15] (data not shown) from this analysis suggest that residual heterogeneity is due to one prospective study[26] that had a larger dose-response slope because of a larger cohort than the other prospective studies.

Table 1—*Studies of Antibiotic Exposure in the First Year of Life and Childhood Asthma*

Source (Year)	Country	Study Design	Population	Age, yr	No.	Covariates*
Celedon et al[23] (2004)	United States	Prospective	Health maintenance organization enrolled from birth	0–5	4,178	Gender; LRI in first year of life
Cohet et al[24] (2004)	New Zealand	Retrospective	Children with notifiable infectious diseases at age 0 to 4 yr recorded in a national database (childhood infections group)	8–9	1,460	Not available
Cohet et al[24] (2004)	New Zealand	Retrospective	Children attending one of 85 primary schools in the greater Wellington region (general population group)	6–7	2,441	Not available
Celedon et al[25] (2002)	United States	Prospective	Children with a parental history of asthma or allergies	0–5	448	Gender; household income; maternal history of asthma
McKeever et al[26] (2002)	United Kingdom	Prospective	Children in the West Midlands General Practice Research Database who were registered with their primary care physician within 3 mo of birth and whose medical history showed at least one consultation	0–11	21,129	Physician consultation rates in the first year of life
Illi et al[27] (2001)	Germany	Prospective	Newborn infants with risk factors for atopy (elevated cord blood IgE $\geq$ 0.9 kU/I or at least two atopic family members)	0–7	937	Not available
Wjst et al[28] (2001)	Germany	Retrospective	Children attending grades 1, 3, or 6	5–14	1,149	Gender; season; community; age; parental education; family history of asthma
Drost et al[29] (2000)	Belgium	Retrospective	Children attending one of 130 primary schools	7–8	1,206	Not available
Wickens et al[30] (1999)	New Zealand	Retrospective	Children attending one of six Rudolf Steiner schools	5–10	263	Age; gender; ethnicity; family size (0, 1, or $\geq$ 2 siblings); family history of asthma; eczema and hay fever; current smoking habit of either parent and during the child's first year of life

*Adjusted for these covariates in dose-response analysis

Figure 3 shows each of the five studies included in the dose-response metaanalysis and their reported adjusted ORs for categories of number of antibiotic courses taken during the first year of life. The log-linear regression fit is shown for each study. From visual examination of these plots, the log-linear model appeared to fit the ORs well. Figure 4 summarizes the exponentiation of the slope of these log-linear regression fits (the OR of asthma risk per course of antibiotics taken during the first year of life) for each study and provides the pooled ORs. The summary OR of the pooled analysis was 1.16 (95% CI, 1.05 to 1.28) for each additional course of antibiotics taken during the first year of life.

Influence Analysis

The pooled OR for the receipt of at least one antibiotic course and the development of asthma for the prospective studies was robust to the exclusion of each study, in that when each prospective study was removed from the metaanalysis, the 95% CI of the pooled OR for the prospective subgroup still covered 1 (results not shown). The other prospective study[26] included in this metaanalysis showed a positive association between antibiotic exposure in the first year of life and asthma risk but could not be included in the pooled analysis as no associated measures were reported.

The pooled OR for the receipt of at least one antibiotic course and the development of asthma for the retrospective studies, however, was less robust to the exclusion of each retrospective study. Table 3 shows the summary of the pooled ORs within the retrospective study subgroup after exclusion of each study. Exclusion of the study of Cohet et al[24] had the most influence over the pooled result, by increasing

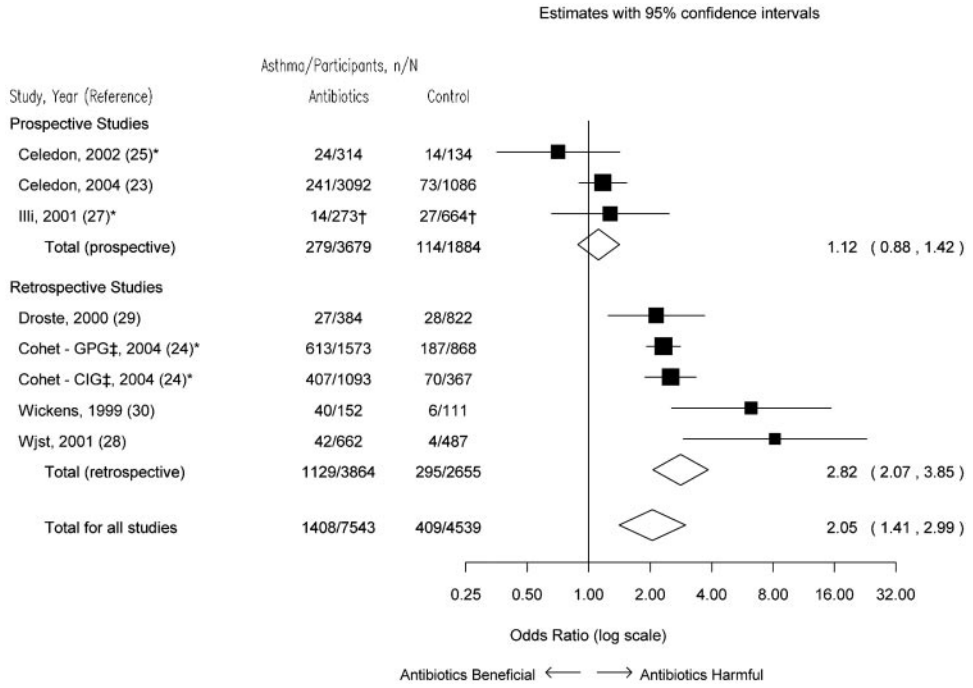

FIGURE 2. ORs with corresponding 95% CIs of the risk of asthma on exposure to at least one course of antibiotics in the first year of life. *Data acquired through correspondence with the author. †Excluded antibiotic courses administered to children for the treatment of LRIs. ‡GPG = general population group; CIG = childhood infections group. The crude number of asthma cases in the antibiotic-exposed group and control group were used to calculate the study-specific unadjusted ORs. ORs were pooled within prospective and retrospective study subgroups using a random-effects analysis, in which the box representing the study-specific unadjusted OR estimate is proportional to the weight of that study in the analysis.

the pooled OR to 4.42 (95% CI, 1.80 to 10.82). As described earlier, removing the studies of Wjst et al[28] or Wickens et al[30] decreased the summary ORs, and removing the studies of Cohet et al[24] and Droste et al[29] study increased the summary ORs.

An influence analysis was not performed on the retrospective study subgroup for the dose-response analysis, as it was only comprised of two studies. Table 3 shows the results of the influence analysis of the prospective subgroup for the dose-response analysis. The 95% CI for the summary dose-response OR for the prospective studies covered 1 regardless of which prospective study was excluded. As expected, excluding the study by McKeever et al[18] from the prospective dose-response metaanalysis was most influential, by decreasing the pooled OR to 1.02 (95% CI, 0.97 to 1.07). This also removed some heterogeneity, as the Q statistic was reduced to 0.68 ($p = 0.41$). Although limited by a small number of studies, we could see no evidence of publication bias from visual inspection of the funnel plot for the analysis of receiving at least one antibiotic course or the dose-response analysis (data not shown).

Table 2—*Pooled ORs and 95% CIs of Asthma Due to Antibiotic Exposure in the First Year of Life*

Analyses	Studies, No.	Patients, No.	Random-Effects Pooled OR (95% CI)	Q Statistic	p Value
At least one antibiotic exposure					
All studies	8	12,082	2.05 (1.41–2.99)	43.44	< 0.01
Prospective studies	3	5,563	1.12 (0.88–1.42)	1.93	0.38
Retrospective studies	5	6,519	2.82 (2.07–3.85)	9.92	0.04
Dose response					
All studies	5	27,167	1.16 (1.05–1.28)	34.44	< 0.01
Prospective studies	3	25,755	1.07 (0.95–1.20)	24.15	< 0.01
Retrospective studies	2	1,412	1.37 (1.18–1.60)	1.48	0.22

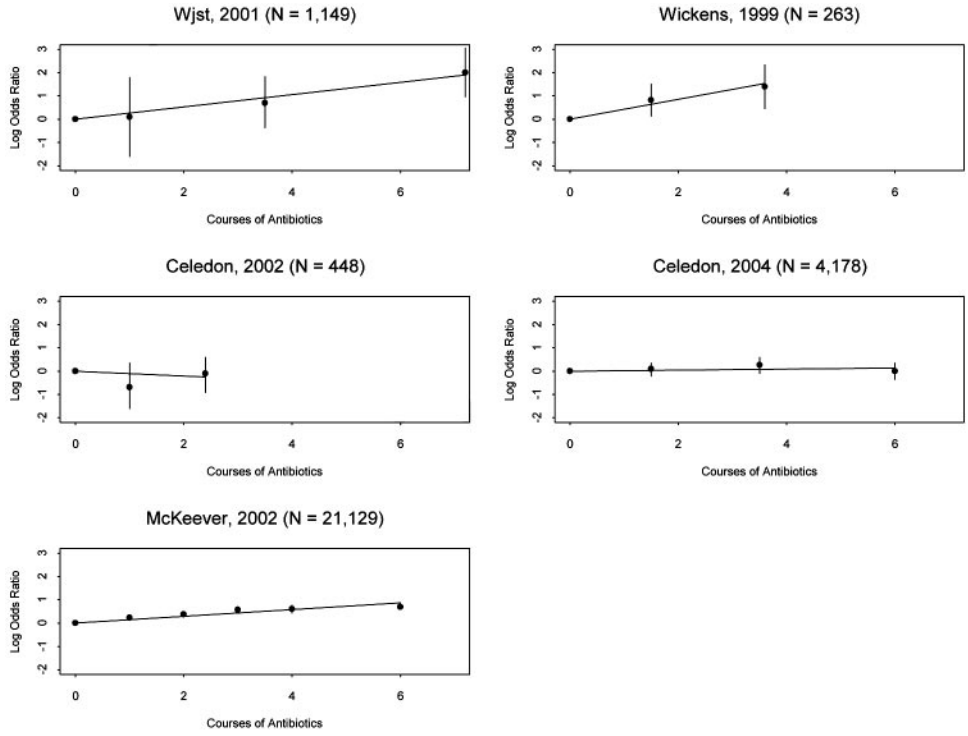

FIGURE 3. Study-specific adjusted ORs with corresponding 95% CIs for the dose-response analysis. The reported adjusted ORs (see Table 1 for adjusted covariates) for each of the five studies included in the dose-response metaanalysis (number of antibiotic courses taken during the first year of life) are plotted separately with the author name, publication year, and number of subjects in the study indicated above the plot. Within each plot, a log-linear regression line through the ORs is displayed.

DISCUSSION

This metaanalysis is the first to address the question of whether antibiotic exposure in the first year of life is associated with the subsequent development of asthma and to address the more specific question of a potential dose-response relationship. Although pooling the results from all of the studies suggests an association between antibiotic exposure and development of asthma (OR, 2.05; 95% CI, 1.41 to 2.99), when the analysis was stratified by the two subtypes of studies (prospective vs retrospective), only the pooled results from the retrospective studies yielded a positive association (OR, 2.82; 95% CI, 2.07 to 3.85). Similarly, for the dose-response analysis, we found the summary OR was lower and nonsignificant for the prospective studies (OR, 1.07; 95% CI, 0.95 to 1.20) as compared to the retrospective studies (OR, 1.37; 95% CI, 1.18 to 1.60).

There are many factors that could explain this difference between the summary ORs derived by pooling the retrospective and the prospective studies such as the methods for ascertainment of asthma, and the ability to adjust for confounding. Unfortunately, we were unable to conduct a subgroup analysis of studies that adjusted for confounders vs those that did not; this is because only two studies[27,29] conducted analyses based on exposure to at least one antibiotic, while the other study[23] conducted a dose-response analysis. Most of the retrospective studies were cross-sectional and relied on parent-completed questionnaires that probed for antibiotic exposure in the first year of life and the subsequent development of asthma. Therefore, the results from these studies could be influenced by recall bias, as parents of children with asthma may be more likely to report an exposure to antibiotics in infancy than those with children without a diagnosis of asthma. In addition, information regarding potential confounders would also be subject to recall bias. In the retrospective studies, asthma was often ascertained through parent-reported physician diagnosis rather than a more objective source, such as administrative or physician records, which were used more commonly in the prospective studies. Finally, the retrospective studies had lower quality scores than the prospective studies, suggesting a poorer quality design.

There are numerous other limitations in the studies included in the metaanalysis. For the analysis investigating the association between the receipt of

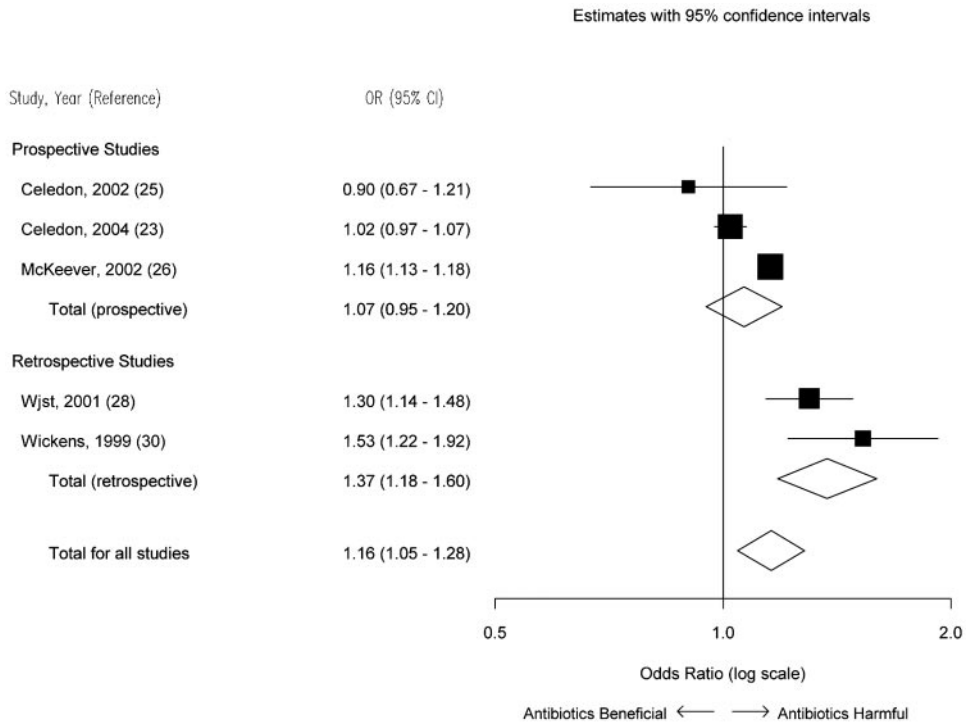

FIGURE 4. ORs with corresponding 95% CIs of the risk of asthma for each additional course of antibiotics taken in the first year of life. Study-specific ORs resulted from fitting a log-linear regression to the reported adjusted ORs within categories of antibiotic exposure (Fig 3). ORs were pooled within prospective and retrospective study subgroups using a random-effects analysis, in which the box representing the study-specific OR estimate is proportional to the weight of that study in the analysis.

at least one antibiotic course and asthma, the number of total participants and asthmatics in any one study was relatively small, particularly in the retrospective studies. The largest study, conducted by Celedon et al,[23] was prospective but only had 4,178 participants. Also, two studies[23,26] evaluated the association between specific antibiotic classes or agents and the subsequent development of asthma, with conflicting results: McKeever et al[26] found an association between certain antibiotic classes and asthma, whereas Celedon et al[23] did not. This discrepancy in their findings may have been due to their different analytic approaches and the adjustment for more potential confounders in the study by Celedon et al.[23] Another significant concern is the issue of reverse causation or confounding by indication, *ie*, the presence of asthma prior to the administration of an antibiotic thereby resulting in more frequent diagnosis of upper respiratory tract infection and the subsequent prescribing of an antibiotic. This concern was addressed by three studies: (1) Celedon et al[23] adjusted for the presence of lower respiratory tract

Table 3—*Influence Analysis of the Pooled ORs From the Retrospective and Prospective Studies*

Analyses	Studies, No.	Patients, No.	Random-Effects Pooled OR (95% CI)	Q Statistic	p Value
At least one antibiotic exposure					
Retrospective studies	5	6,519	2.82 (2.07–3.85)	9.92	0.04
Excluding Cohet et al[24]	3	2,618	4.42 (1.80–10.82)	7.31	0.03
Excluding Droste et al[29]	4	5,313	3.11 (2.11–4.57)	9.60	0.02
Excluding Wjst et al[28]	4	5,370	2.50 (1.99–3.14)	4.71	0.19
Excluding Wickens et al[30]	4	6,256	2.53 (1.95–3.29)	5.77	0.12
Dose response					
Prospective studies	3	25,755	1.07 (0.95–1.20)	24.15	< 0.01
Excluding McKeever et al[26]	2	4,626	1.02 (0.97–1.07)	0.68	0.41
Excluding Celedon et al[25] (2002)	2	25,307	1.07 (0.85–1.34)	2.67	0.10
Excluding Celedon et al[23] (2004)	2	21,577	1.09 (0.97–1.23)	21.78	< 0.01

infections (LRIs) and the number of office visits in the first year of life and found including these attenuated the association; (2) Illi et al[27] excluded antibiotics for LRIs; and (3) Droste et al[29] adjusted for the presence of LRIs in the first 2 years of life. However, most of the included studies did not attempt to investigate the impact that reverse causation would have on their results.

It may be that antibiotic use is not a risk factor in high-risk children (for example, a family history of atopy). To explore this, we conducted a subgroup analysis of studies using high-risk children that revealed that the OR was not significantly associated with antibiotic exposure. However, the difficulty with interpreting this result was that two of the three studies[25,27] were prospective, and their combined number of subjects was far greater than the retrospective study[24] conducted in high-risk children. As such, the lack of association in the high-risk group might be explained by the design of the study (prospective vs retrospective). In order to further investigate this relationship, more studies in the high-risk population need to be conducted.

Future research is required to address the numerous methodologic flaws that are present in the studies performed to date. For example, methods should be employed that will reduce the measurement error in describing antibiotic use and in reducing confounding by indication. This could be performed by conducting the analysis exclusively for antibiotics prescribed for nonrespiratory tract indications (such as skin and soft tissue infections). Also, a post-antibiotic exposure washout period of at least 1 year should be investigated to account for the possibility of asthma cases diagnosed in the second year of life as the impetus for antibiotic therapy in infancy due for early signs of the disease. In addition, future studies examining the relationship between asthma and antibiotic exposure should use validated measures of antibiotic exposure and asthma diagnoses and be conducted in larger, preferably population-based, samples. This would allow for the investigation of exposure to different classes of antibiotic as well as facilitating the further investigation of the dose-response relationship. Due to the expense of conducting assessments, the sample necessary to investigate these questions will likely not be achievable with a prospective clinical study. As such, to determine the risk of asthma following antibiotic use in children stratified by site of infection, type of antibiotics, and other important confounding factors, administrative database studies (similar to the approach taken by McKeever et al[26]) using a population-based approach will likely be the only available mechanism.

Conclusion

The use of antibacterials in the first year of life is associated with the subsequent development of asthma. However, given the limitations in the methodologic quality of the available epidemiologic studies, further large-scale, database-related studies are needed to conclude whether this association is causal or due to reverse causation.

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