Published in final edited form as:

Clin Exp Allergy. 2010 August ; 40(8): 1222–1229. doi:10.1111/j.1365-2222.2010.03539.x.

Relation of early antibiotic use to childhood asthma: confounding by indication?

Y. Su¹, J. Rothers^{1,2}, D. A. Stern¹, M. Halonen^{1,3}, and A. L. Wright^{1,4}

¹Arizona Respiratory Center, Arizona Health Sciences Center

²College of Public Health, University of Arizona, Tucson, AZ, USA

³Department of Pharmacology, University of Arizona, Tucson, AZ, USA

⁴Department of Pediatrics, University of Arizona, Tucson, AZ, USA

Summary

Background—Findings from studies of the relation between early antibiotic use and subsequent asthma have been inconsistent, which may be attributable to methodologic issues.

Objective—Our objective was to assess the impact of confounding by indication on the relation of early antibiotic use to childhood asthma through age 5 in a non-selected birth cohort ($n = 424$).

Methods—Oral antibiotic use was assessed by frequent nurse interviews in the first 9 months of life. Physician-diagnosed active asthma and eczema were assessed by questionnaire at 1, 2, 3, and 5 years, and were considered as ever asthma or ever eczema if positive at any age. Allergen-specific IgE was assessed in plasma at 1, 2, 3, and 5 years. Confounding by indication was investigated by considering the relation of asthma to antibiotic use while controlling for the number of illness visits to a physician in early life.

Results—There was no statistically significant relation of early antibiotic use with physician-diagnosed eczema or allergen-specific IgE. A dose–response relation was evident for antibiotic use with ever asthma (odds ratio [OR] = 1.5, $P = 0.047$). Ever asthma also increased significantly with the number of illness visits to a physician ($P < 0.001$). After adjustment for number of illness visits, antibiotic use showed no relation with asthma.

Conclusions—The relation of asthma to antibiotics in this cohort appears to be an artefact of the strong relation of number of physician visits for illness with both antibiotic use and risk for asthma.

Keywords

antibiotics; asthma; confounding; epidemiology

Correspondence: Anne L. Wright, Arizona Respiratory Center, Arizona Health Sciences Center, University of Arizona, 1501 N. Campbell, Avenue, PO Box 245030, Tucson AZ, 85724, AZ, USA., awright@arc.arizona.edu.

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Introduction

The hygiene hypothesis postulates that reduced exposure to pathogens in the industrialized world may alter immune system development by shifting post-natal immune responses towards the production of T-helper (Th) type 2 cytokines [1, 2]. This hypothesis fuelled interest in the potential relation of childhood asthma with an early use of antibiotics, which alter gut flora and kill bacterial pathogens, potentially reducing the stimulus for antimicrobial immune responses. Several studies have found a positive association between antibiotic use and risk of asthma in childhood [3–8]. For example, in a longitudinal study of Canadian children (5) the risk of asthma at age 7 was significantly higher in those who received four or more courses of antibiotics in their first year of life (adjusted odds ratio [OR] = 1.5, 95% confidence interval [1.1–1.9]). However, relations between antibiotic use and childhood asthma are not consistent in all studies [9–11].

In addition to the lack of consistency of results, methodologic issues also plague the study of these associations. Many of the studies that show a positive relation are retrospective, making them subject to recall bias, such that parents of children may differentially recall early events based on current asthma status. Secondly, few studies address the potential problem of reverse causation, which would occur if the antibiotics were prescribed primarily for symptoms related to undiagnosed asthma, a problem not limited to retrospective studies. Finally, there is the potential for confounding by indication [12], which occurs if the reason for the exposure is itself a risk for the outcome. In this case, confounding by indication would occur if the illnesses for which antibiotics were prescribed (i.e. the indicator for antibiotic use) were themselves risk factors for asthma.

To address these issues, we examined the association between oral antibiotic use in the first 9 months of life and the development of physician-diagnosed asthma, physician-diagnosed eczema, and allergic allergen sensitization by 5 years of age in a non-selected cohort followed prospectively from birth. We specifically investigated confounding by indication by assessing the relation of antibiotic use to asthma after controlling for the number of illness visits to a physician in the first year of life.

Methods

Study design and population

The Infant Immune Study (IIS) is a prospective birth cohort study of the immunologic and exposure predictors of the development of asthma and allergic disease in childhood. Pregnant women were recruited during prenatal visits to 10 obstetric and eight midwife practitioners at five sites in Tucson between 1997 and 2003. Any healthy child born to a woman who planned to seek care for her child through one of 14 collaborating Tucson paediatricians, who spoke English, and who had a telephone, was eligible for the IIS. The only exclusion criteria were: (1) diagnosis of an immune deficiency condition in the mother and (2) plans to leave Tucson. No incentives were provided for participation.

Early illness visits and antibiotics usage

Information on the subjects' early illnesses and corresponding medication use was obtained by nurse interview at 2 weeks (mean age $\pm$ SD, 2.6 $\pm$ 2.1 weeks; $n = 479$), 1 month (1.2 $\pm$ 0.2 months; $n = 344$), 2 months (2.1 $\pm$ 0.2 months; $n=386$), 3 months (3.1 $\pm$ 0.2 months; $n=258$), 4 months (4.2 $\pm$ 0.3 months; $n = 420$), 6 months (6.3 $\pm$ 0.4 months; $n=408$), and 9 months (9.3 $\pm$ 0.5 months; $n = 378$). Parents were asked if the infant had any of the following 11 symptoms since the last interview: wheezing, cough, chest congestion, runny or stuffy nose, hoarseness or sore throat, sneezing, diarrhoea, vomiting, earache, or fever over 100°F. Parents reporting any of these symptoms were then asked whether the child had seen a physician (illness visit), and if so, whether the child took any medicine for the symptoms. Illness visits were tallied to obtain the number of illness visits in the first 9 months.

Children were considered to have used systemic antibiotics in the first 9 months of life if parents reported use of oral antibiotics at any interview. Subjects were considered as not having used oral antibiotics if at least four of the seven interviews were completed with no reported antibiotic use. Ten subjects for whom reports indicated use of topical anti-infective medications only were categorized as not having taken antibiotics.

Information on maternal and paternal history of asthma and household income was obtained by questionnaire at enrolment, while gender and ethnicity were ascertained soon after the infant's birth. Day-care attendance by 3 months of age and infant feeding were also ascertained by nurse interview. Subjects were classified at 3 months as being exclusively breastfed, exclusively formula fed, or as mixed fed (i.e. receiving both human milk and formula). Information on household smoking was obtained by questionnaire at 2 months.

Allergen-specific Immunoglobulin E in the first 5 years of life

Specific IgE was measured for six inhalant allergens (*Alternaria alternata*, *Dermatophagoides farinae*, Bermuda grass, careless weed, olive, and mulberry tree) and two foods (ovalbumin and β -lactoglobulin) in plasma from heparinized blood specimens obtained at 1 year (1.1 $\pm$ 0.1 years; $n=347$), 2 years (2.1 $\pm$ 0.2 years; $n=296$), 3 years (3.2 $\pm$ 0.3 years; $n=286$), and 5 years (5.1 $\pm$ 0.4 years, $n = 274$), as reported previously [13]. These allergens were selected to reflect the main pollen groups present during the five 'seasons' described for Tucson, indoor allergens associated with the development of allergic disease in Tucson and/or other settings, and the major sensitizing agents in young children. A child was considered to be sensitized at each age if he/she showed a detectable IgE response, defined as a plasma concentration ≥ 0.25 IU/ mL, to at least one allergen.

Symptom and illness outcomes

Questionnaires regarding subjects' respiratory symptoms and diagnoses were completed by an adult caregiver when the child was 1 year (1.1 $\pm$ 0.1 years; $n = 423$), 2 years (2.1 $\pm$ 0.2 years; $n = 362$), 3 years (3.2 $\pm$ 0.3 years; $n= 369$), and 5 years old (5.1 $\pm$ 0.4 years; $n= 373$). Children who had been diagnosed by a physician as having asthma and who were reported to have had active symptoms during the past year were categorized as having active MD asthma at each age. Similar criteria were used to define active MD eczema.

Children were included in the 'ever asthma' group if active MD asthma was reported at least once on questionnaires completed at age 1, 2, 3, and/or 5 years. Children were included in the never asthma group if they had no reports of active asthma on any completed questionnaire. 'Ever eczema' was similarly defined. 'Ever sensitization' was defined as detectable allergen-specific IgE at age 1, 2, 3, or 5 years.

Statistical analysis

Characteristics of subjects with and without antibiotic exposure were compared using Fisher's exact test for categorical variables and Student's *t*-tests for means of normally distributed continuous variables. Fisher's exact test was also used to assess relations of early antibiotic use to active asthma, eczema, and specific allergen sensitization at age 1, 2, 3, and 5 years, and to prevalence of ever asthma, eczema, and sensitization by age 5. The relation of number of courses of antibiotics to ever asthma was assessed by trend chi-square. Odds ratios were calculated using logistic regression in order to adjust the relation between antibiotic use and allergic outcomes for confounders. To address the potential for confounding by indication, the relation of asthma prevalence to the number of visits to a physician was assessed for children who did and did not receive antibiotics. Finally, logistic regression was used to determine ORs for asthma with respect to categories of subjects defined by number of illness visits and antibiotic use.

The data were analysed using SAS 9.2 (SAS Institute, Cary, NC, USA), SPSS 15.0 (SPSS Inc., Chicago, IL, USA), and STATA 10.0 (StataCorp, College Station, TX, USA). Statistical significance was defined by a two-sided α level of 0.05. This research was approved by the Institutional Review Board of the University of Arizona and informed consent was obtained for all subjects.

Results

Participation

A total of 812 expectant mothers were asked to participate in the study. Compared with women who chose not to participate ($N = 328$), women who enrolled their children in the study ($N = 484$) had more years of education (mean: 15.2 vs. 14.6, $P = 0.006$) and fewer previous pregnancies (mean: 1.1 vs. 1.4, $P = 0.002$). They were also more likely to plan to work outside of the home after the child's birth (62.2% vs. 54.8%, $P = 0.041$), to have ever had asthma (19.5% vs. 10.7%, $P = 0.003$), and to plan to breastfeed (92.3% vs. 87.9%, $P = 0.048$) than mothers who did not participate. Participants did not differ from non-participants with respect to maternal or paternal age, paternal education, marital status, ethnicity, or maternal smoking (supporting information Table S1).

Antibiotic use

A total of 424 children were included in the analysis of relations between antibiotic use and asthma-related outcomes after excluding eight subjects who were diagnosed with asthma before receiving antibiotics and 50 children who either did not have information on asthma status or who had fewer than four nurse interviews in the first 9 months. Subjects included in the analysis were significantly more likely to come from higher income families, to be non-

Hispanic Caucasians, to have been breastfed at 3 months, to have had no household smokers at 2 months, and to have not attended day care by 3 months, compared with excluded subjects ($N=58$, Table S2).

Almost one-third of the subjects (32.1%, 136/424) used oral antibiotics at least once during the first 9 months of life. The prevalence of antibiotic use increased with age, from 1.6% at 1 month to 11.6% at 6 months and 24.7% at 9 months. There was a large amount of overlap between antibiotic use and physician illness visits for earache: nearly all children who used antibiotics took at least one course for earache (95.6%, 130/136), and the majority of children who had a physician visit for earache in the first 9 months used antibiotics (94.2%, 129/137). No children used antibiotics exclusively for wheezing, and very few reported antibiotic use for chest congestion, cough, or fever. Most subjects using antibiotics took only one course (73.5%, 100/136), with relatively few using antibiotics for two (23.5%, 32/136) or more (2.9%, 4/136) illness episodes. None of the consecutive usages appeared to be for the same prescription, as the shortest interval between antibiotic courses was 3 weeks. The most commonly used antibiotics were penicillin derivatives, with 87.5% reporting at least one course of these medications (119/136).

Antibiotic use in the first 9 months of life was more common among boys, those who were formula-fed at 3 months or exposed to household smoking at 2 months, those attending day care by 3 months, and those who lacked paternal history of asthma (Table 1). No association was found between antibiotic use and the subject's ethnicity, maternal asthma, or annual household income.

Prevalence of asthma and allergic outcomes by age

The prevalence of physician-diagnosed active asthma and detection of allergen-specific IgE increased with age, whereas the prevalence of physician-diagnosed active eczema decreased with age (Table 2).

Relationship between antibiotic use and allergic outcomes

There was no statistically significant relation of antibiotic use with active physician-diagnosed asthma, active physician-diagnosed eczema, or presence of allergen-specific IgE at any single age (Table 3). Similarly, there was no significant relation of antibiotic use with prevalence of ever eczema or ever detectable IgE by age 5.

In contrast, there was a relation of any antibiotic use to ever asthma of borderline significance ($P = 0.075$), and the relation was strengthened when the number of courses of antibiotics administered in the first 9 months ($P = 0.016$, Fig. 1) was considered. Even after adjustment for gender and feeding status (potential confounders related to both antibiotic use and prevalence of asthma, Table 1 and Table S3), odds for asthma were still significantly increased in association with number of antibiotic courses as a continuous variable ($OR_{unadjusted} = 1.5$, $P = 0.047$; $OR_{adjusted} = 1.5$, $P = 0.043$). The relation with number of courses of antibiotics was not significant for ever eczema or ever detectable specific IgE (data not shown).

Confounding by number of illness visits

As antibiotics can be prescribed only for illnesses for which a doctor is consulted, we assessed the number of illness visits in the first 9 months of life as a potential confounder. There was a direct association between the number of illness visits and antibiotic use, with percent using antibiotics being 0%, 35.5%, 46.9%, and 78.3% for children with no, one, two, and three or more illness visits ($P < 0.001$). Similarly, there was a dose-response relation between ever asthma and number of illness visits in the first 9 months of life, with the prevalence of ever asthma being 7.8%, 8.6%, 17.4%, and 21.7% for those with no illness visits and one, two, or three illness visits, respectively ($P = 0.015$). These findings raise the question of whether the dose-response relation of number of antibiotic courses to asthma prevalence was confounded by the number of illness visits.

To investigate this possibility, we assessed the relation between number of illness visits in the first 9 months and ever asthma, stratified by antibiotic use (Fig. 2). The increase in ever asthma associated with number of early-life illness visits was statistically significant only for subjects who were not prescribed antibiotics. However, an increase was observed for both groups and there was no statistical evidence of interaction ($P_{\text{interaction}} = 0.4$). A similar pattern was evident when only visits for symptoms associated with respiratory illnesses (any combination of cough, chest congestion, wheeze, sore throat, sneezing, or runny nose) were considered. In contrast, there was no relation between asthma prevalence and illness visits for gastrointestinal illnesses (vomiting or diarrhoea), either for the group as a whole or when stratified by antibiotic use (data not shown).

When number of illness visits and antibiotic use were entered together into a logistic model as separate variables, only illness visits showed a significant relation with asthma (OR: 1.5 [1.1, 2.1], $P = 0.016$). Antibiotic use was non-significant in models adjusted for number of illness visits, regardless of whether it was defined as 'ever use' (OR: 1.2 [0.6, 2.3], $P = 0.7$) or 'number of courses' (OR: 1.1 [0.7, 1.9], $P = 0.6$). To further investigate the possibility of confounding, a combined variable including both antibiotic use (yes/no) and number of illness visits was created and entered into a logistic regression model. Compared with children who had no illness visits and no antibiotics, both unadjusted and adjusted ORs for asthma were increased for children who had multiple illness visits, regardless of antibiotic usage (Table 4).

There was no relation of the other allergic outcomes (eczema or specific IgE) with number of illness visits and nor any evidence that illness visits played a confounding role in the relations between these outcomes and early antibiotic usage (data not shown).

Potential misclassification of antibiotics exposure

As the nurses prompted parents to recall all illnesses since the previous interview, only children who lacked the seventh (9 month) interview may be misclassified with regard to exposure to antibiotics, as data were not available on the final interval. To determine whether our results were biased by including children who lacked the seventh interview, we conducted a subset analysis on children who had at least four interviews including the

seventh ($n = 365$). Results, including direction of relations and significance levels, did not change as a result of restricting the analysis to this subset.

Discussion

This prospective study initially found that antibiotic use in the first 9 months of life was associated with an increase in the prevalence of asthma by age 5, with a significant dose–response relation evident for the number of antibiotic courses in the first 9 months. However, we also found that the prevalence of asthma increased with the number of illness visits in the first 9 months, regardless of the use of antibiotics. When analyses were adjusted for the number of illness visits in the first 9 months, the asthma–antibiotics relation was no longer significant. Antibiotic use showed no relation to either physician-diagnosed eczema or allergic sensitization. Based on these observations, it seems possible that the relation of asthma to antibiotics in this cohort and potentially others is an artefact of the fact that both antibiotic use and risk for asthma are associated with number of illness visits in the first year of life.

A number of early studies reported an association between antibiotic use in early life and asthma in childhood [3, 4, 6–8, 14, 15], though in some cases, relations were limited to specific subgroups of children. In one cross-sectional study of 7–8-year-old Belgian children, for example, antibiotic use in the first year of life was associated with asthma (OR: 2.3 [1.1–5.1]), hayfever (OR: 2.8 [1.5–5.1]), and eczema (OR: 1.6 [1.0–2.6]) but only among children with a familial history of hayfever [4]. However, all of these studies were cross sectional and retrospective, raising questions about potential recall bias.

More recent prospective studies have suggested a positive relation between asthma and antibiotics, but again results are mixed. A large Canadian study [5] that used health care and prescription data bases found that children who received antibiotics in the first year of life had elevated odds of having asthma at age 7. Further, the odds were highest in children who received four or more courses of antibiotics. More recently, Marra et al. [16] utilized an administrative health data base that included information on all live births in British Columbia from 1997 to 2003. The date of asthma diagnosis was defined as the first of three events: (1) a hospital discharge for asthma, (2) two medical claims for asthma (ICD-9 493) within a moving 12-month period, or (3) two prescriptions for a known asthma medication within a moving 12-month period. Antibiotic use in the first year of life was associated with significantly increased risk of asthma between 2–3, 3–5, and 5–9 years of age, after adjusting for a long list of potential factors. However, a smaller prospective study found no relation between antibiotic use and asthma through age 5 [17].

The methodologic challenge for all these studies is the potential for confounding by indication, which occurs if the reason for the exposure is itself a risk for the outcome. In most studies of asthma, confounding by indication has been interpreted with reference to respiratory illnesses, because antibiotics are often prescribed for LRIs, which are themselves associated with increased risk for asthma [12]. Thus, other investigations of this issue [5, 16–18] have focused on the distinction between respiratory vs. non-respiratory illnesses with the assumption that if associations were seen in the latter group as well as in the former,

there would be no confounding by indication. Kozyrskyj et al. [5] showed that the risk of asthma associated with frequency of antibiotic use was still elevated when the relation was adjusted for lower respiratory tract illnesses. In contrast, Wickens et al. [18] showed that when the relation of antibiotic use to asthma was adjusted for chest infections, the relation became nonsignificant and only chest infections were associated with a significant asthma risk.

This paper contributes to the discussion by expanding the consideration of confounding by indication beyond issues pertaining specifically to respiratory illnesses, to investigate whether the illnesses for which antibiotics were prescribed (i.e. the indicator for antibiotic use) are themselves risk factors for asthma. Consistent with a nonspecific relation, our analyses indicate that asthma prevalence is increased in association with number of visits for any illness, being highest among children with three or more illness visits in the first 9 months of life. Stratified analyses indicated that the relation of illness visits to asthma was not limited to those who were administered antibiotics. In fact, the relation of illness visits to asthma risk was stronger for subjects who did not receive any antibiotics than for subjects who did receive these medications. Furthermore, the relation of asthma to antibiotics, whether defined as 'ever used' or by number of courses, was no longer significant after controlling for the number of illness visits. Other studies that show a dose-response relation between number of courses of antibiotics and asthma [5, 8] may similarly be measuring the increased risk of asthma associated with frequent illness visits rather than any causal relation with antibiotic exposure. Although Kozyrskyj et al. [5] adjusted for the number of illnesses, to our knowledge, this analysis is the first to show the relation of antibiotic use to asthma according to the number of illness visits.

A recent report [16] that found a small but significant increase in asthma among children who received antibiotics in the first year of life would seem to be the final word on this subject, given that the sample size was over 250 000. However, two aspects of the analysis make the results less than persuasive. First, in models adjusted for the number of physician visits, the effect size for antibiotics usage is small ($HR = 1.12$) compared with the effect sizes for other factors, such as increasing numbers of physician visits (HR s ranging from 1.19 to 2.88 for low to high number of visits). Secondly, models showing a dose-response relation between number of prescriptions of antibiotics and asthma do not control for number of physician visits, raising the possibility that this effect is attributable to the strong relation of number of physician visits to asthma.

A final observation from the present study pertinent to this discussion is that there was no relation of antibiotic use in the first year of life with objective measures of sensitization. Similarly, there was no association of antibiotics with diagnosed eczema, which is a strong risk factor for asthma [19]. Two other studies that also included objective assessment of sensitization similarly found no significant relation with antibiotic use [17, 18]. Given that allergic sensitization is a strong risk factor for asthma from mid-childhood to later life [20], this consistently negative relation may suggest that antibiotic use is not associated with allergic asthma, the primary form of asthma in older children. Unfortunately, none of the large health record-based studies obtained objective information on atopy [5, 16].

Our finding that the frequency of illness visits is associated with elevated risk for asthma can be interpreted in several ways. First, illnesses for which a physician is consulted tend to be more severe than other illnesses. Thus, children with frequent illness visits may either be more vulnerable to illness in general or more likely to mount an exaggerated immune response to infections, either of which may be associated with susceptibility to asthma. Alternatively, the link between illness visits and asthma may be behavioural. To be diagnosed with asthma requires that the child is seen by a doctor. Thus, children who are seen more frequently by the physician have more opportunity for any respiratory symptoms they experience to be diagnosed as asthma [21]. As seeing a doctor is necessary for a prescription for an antibiotic, children who see the doctor frequently are also at an increased risk of taking antibiotics, potentially leading to a spurious relationship.

This study has certain limitations. First, our information on antibiotic use is limited to the first 9 months of life and no data on its use are available after that age. Thus, our findings are based on the assumption either that antibiotic use after 9 months does not alter asthma risk or that use patterns are the same as before after that age. This same caveat would apply to other studies, regardless of the age cut-off used. Second, we lacked detailed information on the type of antibiotics used. Studies have shown that the use of broad-spectrum cephalosporins can lead to marked disruptions of intestinal microflora [22–24]. If this type of antibiotic were associated with elevated asthma risk, combining the groups may have masked the relation. Although the prevalence of asthma and allergic outcomes are roughly comparable to those shown in other populations of children at these ages [4, 8, 9, 25], we might have found stronger associations with antibiotic use had we followed children past age 5. Compared with previous studies, prevalence of antibiotic use (32%) was relatively low in our population, although this is consistent with national trends towards reduced use of antibiotics [26]. Nevertheless, had a higher proportion of our population been exposed to antibiotics, a relationship with asthma independent of doctor visits might have become evident. Because some study subjects were excluded from our analysis due to lack of sufficient data, we cannot be sure that the relations reported herein would hold if the omitted children were included. However, as we failed to find evidence of confounding for any of the demographic or environmental variables that we assessed, it is unlikely that this exclusion has biased our results. Finally, because of the overlap between earache and antibiotic use, we were not able to distinguish relations between earache and asthma from relations between antibiotics and asthma. Nevertheless, this prospective study utilized frequent interviews to reduce recall bias, and obtained detailed information on the timing of antibiotic use and diagnosis of asthma, thereby reducing reverse causation as a possible bias, while including children whose asthma was diagnosed after the 9 month point but still as early as the latter part of the first year of life.

In conclusion, this study suggests that at least a major portion of the relation between antibiotic use and childhood asthma observed in some studies may be an artefact of the strong relation of illness visits to a doctor to both antibiotic use and risk for asthma diagnosis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The authors thank the study nurses, Jody Mallie and Heidi Erickson, for data collection on study subjects, I. Carla Lohman, Amber Spangenberg, Sara Mobley, and Dayna Anderson for sample processing and IgE measurements, Susan Solomon for laboratory database creation and maintenance, and Bruce Saul for assistance with data analysis.

Declaration of all sources of funding: Supported by grants from the Arizona Disease Control Research Commission, Science Foundation of Arizona, and the National Institutes of Health (AI 42268 and AI61811). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institute of Allergy And Infectious Diseases, the National Institutes of Health, Science Foundation Arizona, or the Arizona Disease Control Research Commission.

References

1. Strachan DP. Hay fever, hygiene, and household size. *Br Med J*. 1989; 299:1259–60. [PubMed: 2513902]
2. Martinez FD. The coming-of-age of the hygiene hypothesis. *Respir Res*. 2001; 2:129–32. [PubMed: 11686875]
3. Cohet C, Cheng S, MacDonald C, et al. Infections, medication use, and the prevalence of symptoms of asthma, rhinitis, and eczema in childhood. *J Epidemiol Community Health*. 2004; 58:852–7. [PubMed: 15365112]
4. Droste JH, Wieringa MH, Weyler JJ, Nelen VJ, Vermeire PA, Van Bever HP. Does the use of antibiotics in early childhood increase the risk of asthma and allergic disease? *Clin Exp Allergy*. 2000; 30:1547–53. [PubMed: 11069562]
5. Kozyrskyj AL, Ernst P, Becker AB. Increased risk of childhood asthma from antibiotic use in early life. *Chest*. 2007; 131:1753–9. [PubMed: 17413050]
6. McKeever TM, Lewis SA, Smith C, et al. Early exposure to infections and antibiotics and the incidence of allergic disease: a birth cohort study with the West Midlands General Practice Research Database. *J Allergy Clin Immunol*. 2002; 109:43–50. [PubMed: 11799364]
7. von Mutius E, Illi S, Hirsch T, Leupold W, Keil U, Weiland SK. Frequency of infections and risk of asthma, atopy and airway hyperresponsiveness in children. *Eur Respir J*. 1999; 14:4–11. [PubMed: 10489821]
8. Wickens K, Pearce N, Crane J, Beasley R. Antibiotic use in early childhood and the development of asthma. *Clin Exp Allergy*. 1999; 29:766–71. [PubMed: 10336592]
9. Celedon JC, Fuhlbrigge A, Rifas-Shiman S, Weiss ST, Finkelstein JA. Antibiotic use in the first year of life and asthma in early childhood. *Clin Exp Allergy*. 2004; 34:1011–6. [PubMed: 15248843]
10. Celedon JC, Litonjua AA, Ryan L, Weiss ST, Gold DR. Lack of association between antibiotic use in the first year of life and asthma, allergic rhinitis, or eczema at age 5 years. *Am J Respir Crit Care Med*. 2002; 166:72–5. [PubMed: 12091174]
11. Illi S, von Mutius E, Lau S, et al. Early childhood infectious diseases and the development of asthma up to school age: a birth cohort study. *Br Med J*. 2001; 322:390–5. [PubMed: 11179155]
12. Kummeling I, Thijs C. Reverse causation and confounding-by-indication: do they or do they not explain the association between childhood antibiotic treatment and subsequent development of respiratory illness? *Clin Exp Allergy*. 2008; 38:1249–51. [PubMed: 18564329]
13. Rothers J, Stern DA, Spangenberg A, Lohman IC, Halonen M, Wright AL. Influence of early day-care exposure on total IgE levels through age 3 years. *J Allergy Clin Immunol*. 2007; 120:1201–7. [PubMed: 17854882]
14. Wjst M, Hoelscher B, Frye C, Wichmann HE, Dold S, Heinrich J. Early antibiotic treatment and later asthma. *Eur J Med Res*. 2001; 6:263–71. [PubMed: 11432798]
15. Foliaki S, Pearce N, Bjorksten B, Mallol J, Montefort S, von Mutius E. Antibiotic use in infancy and symptoms of asthma, rhinoconjunctivitis, and eczema in children 6 and 7 years old:

- international study of asthma and allergies in childhood phase III. *J Allergy Clin Immunol*. 2009; 124:982–9. [PubMed: 19895986]
16. Marra F, Marra CA, Richardson K, et al. Antibiotic use in children is associated with increased risk of asthma. *Pediatrics*. 2009; 123:1003–10. [PubMed: 19255032]
17. Kusel MM, de Klerk N, Holt PG, Sly PD. Antibiotic use in the first year of life and risk of atopic disease in early childhood. *Clin Exp Allergy*. 2008; 38:1921–8. [PubMed: 19037966]
18. Wickens K, Ingham T, Epton M, et al. The association of early life exposure to antibiotics and the development of asthma, eczema and atopy in a birth cohort: confounding or causality? *Clin Exp Allergy*. 2008; 38:1318–24. [PubMed: 18727794]
19. Burgess JA, Lowe AJ, Matheson MC, Varigos G, Abramson MJ, Dharmage SC. Does eczema lead to asthma? *J Asthma*. 2009; 46:429–36. [PubMed: 19544160]
20. Martinez FD, Wright AL, Taussig LM, Holberg CJ, Halonen M, Morgan WJ. Asthma and wheezing in the first six years of life. The group health medical associates. *N Engl J Med*. 1995; 332:133–8. [PubMed: 7800004]
21. Wright AL, Stern DA, Kauffmann F, Martinez FD. Factors influencing gender differences in the diagnosis and treatment of asthma in childhood: the Tucson children's respiratory study. *Pediatr Pulmonol*. 2006; 41:318–25. [PubMed: 16477658]
22. Bonnemaïson E, Lanotte P, Cantagrel S, et al. Comparison of fecal flora following administration of two antibiotic protocols for suspected maternofetal infection. *Biol Neonate*. 2003; 84:304–10. [PubMed: 14593241]
23. Bennet R, Eriksson M, Nord CE. The fecal microflora of 1–3-month-old infants during treatment with eight oral antibiotics. *Infection*. 2002; 30:158–60. [PubMed: 12120942]
24. Edlund C, Nord CE. Effect on the human normal microflora of oral antibiotics for treatment of urinary tract infections. *J Antimicrob Chemother*. 2000; 46(Suppl. 1):41–8. discussion 63–5.
25. Johnson CC, Ownby DR, Alford SH, et al. Antibiotic exposure in early infancy and risk for childhood atopy. *J Allergy Clin Immunol*. 2005; 115:1218–24. [PubMed: 15940137]
26. Grijalva CG, Nuorti JP, Griffin MR. Antibiotic prescription rates for acute respiratory tract infections in US ambulatory settings. *J Am Med Assoc*. 2009; 302:758–66.

Fig. 1.
Prevalence of asthma by 5 years by number of antibiotic courses in the first 9 months of life.
 P for trend = 0.023.

Fig. 2. Prevalence of ever asthma by number of illness visits in the first 9 months of life for children who did and did not receive antibiotics (AB) in the first 9 months.

Table 1
Percent of subjects using antibiotics during the first 9 months of life by demographic and exposure characteristics

	Antibiotics % (<i>n</i> +/ <i>n</i> [†])	<i>P</i> -value*
Gender		
Female	27.9 (62/222)	0.061
Male	36.6 (74/202)	
Ethnicity		
Non-Hispanic White	29.4 (78/265)	0.134
Hispanic/other	36.5 (58/159)	
Feeding at 3 months		
Exclusive breast-milk	15.1 (16/106)	<0.001
Mixed fed	33.7 (65/193)	
Exclusive formula	43.9 (54/123)	
Maternal asthma		
No	31.8 (104/327)	0.509
Yes	27.7 (23/83)	
Paternal asthma		
No	33.0 (107/324)	0.026
Yes	18.5 (12/65)	
Household smoking at 2 months		
No	28.8 (98/340)	0.011
Yes	45.1 (32/71)	
Any day care by 3 months		
No	27.0 (62/230)	0.002
Yes	43.5 (57/131)	
Household annual income		
<25K	28.8 (17/59)	0.689
25–45K	34.7 (34/98)	
>45K	30.5 (73/239)	

* *P*-value obtained by Fisher's exact test.

[†] Total N's vary as data on some subjects are missing for some factors.

Table 2

Prevalence of asthma and allergic outcomes by age

	(n+/n)				
	Year 1	Year 2	Year 3	Year 5	Ever to age 5
MD-diagnosed active asthma	1.5 (6/408)	4.3 (15/353)	7.2 (26/362)	10.8 (39/360)	11.8 (50/424)
MD-diagnosed active eczema	20.8 (85/408)	16.0 (56/350)	14.1 (51/362)	11.5 (41/356)	31.6 (134/424)
Detectable allergen-specific IgE	19.4 (65/335)	29.1 (84/289)	36.9 (103/279)	47.3 (124/262)	50.8 (202/398)

Table 3
Bivariate relation of antibiotics with asthma, eczema, and allergen-specific IgE

<i>(n+ln)</i>					
Antibiotics	Year 1	Year 2	Year 3	Year 5	Ever
MD-diagnosed active asthma					
No	1.1 (3/282)	3.7 (9/242)	6.0 (15/249)	8.8 (22/249)	9.7 (28/288)
Yes	2.4 (3/126)	5.4 (6/111)	9.7 (11/113)	15.3 (17/111)	16.2 (22/136)
<i>P</i> -value	0.378	0.570	0.271	0.097	0.075
MD-diagnosed active eczema					
No	18.8 (53/282)	15.0 (36/240)	13.3 (33/249)	11.4 (28/246)	29.5 (85/288)
Yes	25.4 (32/126)	18.2 (20/110)	15.9 (18/113)	11.8 (13/110)	36.0 (49/136)
<i>P</i> -value	0.147	0.438	0.516	1.000	0.181
Detectable allergen-specific IgE					
No	18.8 (44/234)	27.9 (56/201)	38.1 (74/194)	47.2 (83/176)	50.4 (137/272)
Yes	20.8 (21/101)	31.8 (28/88)	34.1 (29/85)	47.7 (41/86)	51.6 (65/126)
<i>P</i> -value	0.655	0.574	0.590	1.000	0.830

Table 4
Odds ratios (OR) for ever asthma by number of illness visits and use of antibiotics

Number of illness visits	% with asthma (n/N)	OR (95% CI)	P-value	Adjusted OR* (95% CI)	P-value
No antibiotics					
0 MD visit	7.8 (10/128)	(Ref)		(Ref)	
1 MD visit	6.1 (6/98)	0.8 (0.3, 2.2)	0.624	0.7 (0.3, 2.1)	0.582
2 MD visits	17.3 (9/52)	2.5 (0.9, 6.5)	0.067	2.7 (1.0, 7.2)	0.048
3 MD visits	30.0 (3/10)	5.1 (1.1, 22.6)	0.034	4.5 (1.0, 20.6)	0.055
Antibiotics used					
1 MD visit	13.0 (7/54)	1.8 (0.6, 4.9)	0.280	1.9 (0.7, 5.4)	0.238
2 MD visits	17.4 (8/46)	2.5 (0.9, 6.7)	0.074	2.2 (0.8, 6.3)	0.142
3 MD visits	19.4 (7/36)	2.8 (1.0, 8.1)	0.050	3.7 (1.2, 11.3)	0.020

* Adjusted for 3-month feeding practice and gender.