

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

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Background: Phase III of the International Study of Asthma and Allergies in Childhood measured the global prevalence of symptoms of asthma, rhinoconjunctivitis, and eczema in children.

Objective: To investigate the associations between the use of antibiotics in the first year of life and symptoms of asthma, rhinoconjunctivitis, and eczema in children 6 and 7 years old.

Methods: Parents or guardians of children 6 and 7 years old completed written questionnaires on current symptoms and possible risk factors. Prevalence odds ratios (ORs) were estimated by using logistic regression.

Results: A total of 193,412 children from 71 centers in 29 countries participated. Reported use of antibiotics in the first year of life was associated with an increased risk of current asthma symptoms (wheezing in the previous 12 months) with an OR (adjusted for sex, region of the world, language, and per capita gross national income) of 1.96 (95% CI, 1.85-2.07); this fell to 1.70 (1.60-1.80) when adjusted for other risk factors for asthma. Similar associations were observed for severe asthma symptoms (OR, 1.82; 95% CI, 1.67-1.98), and asthma ever (OR, 1.94; 95% CI, 1.83-2.06). Use of antibiotics in the first year of life was also associated, but less strongly, with increased risks of current symptoms of rhinoconjunctivitis (OR, 1.56; 95% CI, 1.46-1.66) and eczema (OR, 1.58; 95% CI, 1.33-1.51).

Conclusion: There is an association between antibiotic use in the first year of life and current symptoms of asthma, rhinoconjunctivitis, and eczema in children 6 and 7 years old. Further research is required to determine whether the observed associations are causal or are a result of

confounding by indication or reverse causation. (*J Allergy Clin Immunol* 2009;124:982-9.)

Key words: Antibiotics, ISAAC, asthma, rhinoconjunctivitis, eczema

The hygiene hypothesis^{1,2} postulates that growing up in a more hygienic environment with less microbial exposure may enhance atopic (T_H2) immune responses, whereas microbial pressure would drive the response of the immune system—which is known to be skewed in an atopic T_H2 direction during fetal and perinatal life—in a T_H1 direction and away from its tendency to develop atopic immune responses.^{3,4} This would protect against atopy and allergic (but not nonallergic) asthma. A corollary of the hygiene hypothesis is that antibiotic use may increase the risk of asthma by reducing the protective effect of microbial exposure, for example, through disruption of the normal gut microbiota,^{5,6} which constitute a complex ecosystem.⁷ However, the epidemiologic evidence of an association between exposure to antibiotics and the development of asthma has been conflicting,⁸⁻²⁰ with most positive associations coming from cross-sectional rather than prospective studies.²¹ One possible explanation for these inconsistencies is that negative studies have generally included any antibiotic use and/or have involved a relatively broad age range, whereas the positive studies have generally been limited to age of less than 2 years and to broad-spectrum antibiotics.^{22,23}

To investigate further the hypothesis that antibiotic use may be linked to subsequent risks of asthma, rhinitis, and eczema, we have studied the associations between parental-reported antibiotic use in the first year of life and current symptoms of asthma, rhinoconjunctivitis, and eczema in children 6 and 7 years old from Phase III of the International Study of Asthma and Allergies in Childhood (ISAAC) study.²⁴⁻²⁶

METHODS

Phase III of ISAAC is a multicenter, multicountry, cross-sectional study of 2 age groups of schoolchildren (children 6-7 years old and adolescents 13-14 years old) chosen from a random sample of schools in a defined geographical area.^{25,27} The Phase III survey included 2 standardized questionnaires. The first symptom questionnaire obtained data on symptoms of asthma, rhinoconjunctivitis, and eczema, and was identical to that used in Phase 1 of the ISAAC study.²⁸⁻³¹ The second environmental questionnaire obtained data on a wide range of possible risk factors for the development of asthma and allergic disorders.³² The current analysis is restricted to the younger age group because it involved parental reporting and it was therefore possible to ask about use of medications in the first year of life; the questionnaire for the older age group was self-completed, and it was therefore not considered feasible to ask about exposures in the first year of life. For the younger age group, the questionnaire included questions on age, sex, family size, birth order,

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Abbreviations used

ISAAC: International Study of Asthma and Allergies in Childhood
OR: Odds ratio

antibiotic use in the first year of life, breast-feeding, birth weight, current diet, heating and cooking fuels, exercise, pets, socioeconomic status, immigration status, environmental tobacco smoke, traffic pollution, and paracetamol use in the first year of life and in the past 12 months. The complete questionnaire can be found on the ISAAC Web site (<http://isaac.auckland.ac.nz>).

The question relating to antibiotic use was “In the first 12 months of life, did your child have any antibiotics?” (yes/no).

Symptoms of current wheeze were determined by positive answers to the written question “Has your child had wheezing or whistling in the chest in the past 12 months?”

Current symptoms of rhinoconjunctivitis were determined by positive answers to 2 questions: “In the past 12 months has your child had a problem with sneezing or a runny or blocked nose when he/she DID NOT have a cold or the flu?” If yes, “In the past 12 months has this nose problem been accompanied by itchy watery eyes?”

Current symptoms of eczema were determined by positive answers to 2 questions: “Has your child had this itchy rash at any time in the past 12 months?” and “Has this itchy rash at any time affected any of the following places—the folds of the elbows, behind the knees, in front of the ankles, under the buttocks, or around the neck, ears or eyes?” These questions were preceded by the question “Has your child ever had an itchy skin rash which was coming and going for at least 6 months?”

Severe asthma symptoms were defined as wheezing causing sleep disturbance, or wheezing limiting speech, or 4 or more attacks of wheezing in the past 12 months.

Adherence to the ISAAC protocol was assessed, and centers with serious discrepancies were excluded (centers with response rates <60% and centers with fewer than 1000 participants). Minor deviations were footnoted.^{24,28,30,31}

Data analysis

To be included in the analysis, centers were required to have $\geq 70\%$ of participants with data on reported antibiotic use (4 centers were accordingly excluded). For the initial analyses (adjusted for sex, region, language, and gross national income, but not other risk factors), we also excluded children with missing data on antibiotic use or sex. Prevalence odds ratios (ORs)³³ were calculated by using generalized linear mixed models with a binomial distribution and logit and with the centers modeled as a random effect. All analyses were adjusted for sex, region of the world (9 categories: Africa, Asia Pacific, Eastern Mediterranean, Latin America, North America, Northern and Eastern Europe, Oceania, Indian Subcontinent, and Western Europe), language (8 categories: Arabic, Chinese, English, Hindi, Indonesian, Portuguese, Spanish, and other), and per capita gross national income (4 categories: classified by the World Bank as low, lower-middle, upper-middle, and upper³⁴). The regression models allowed for the sampling by schools by scaling the size of the sample by the design effect.

Further multiple regression analyses were conducted to investigate whether the associations between symptoms and antibiotic use were confounded by other asthma risk factors for which information was collected in the environmental questionnaire, and which had shown associations with asthma symptoms in univariate analyses. The covariates included in these further multiple regression analyses were maternal education (4 categories: none, primary, secondary, and tertiary), paracetamol use in the first year of life (yes/no), ever breast-fed (yes/no), parental smoking (maternal yes/no; paternal yes/no), current diet (fruit 3+/wk, 1-2/wk, less; vegetables 3+/wk, 1-2/wk, less; pulses 3+/wk, 1-2/wk, less), and siblings (younger yes/no; older yes/no). For inclusion in these further analyses, centers were required to have at least 70% data available for all covariates, and we then removed the blank observations, giving us a data set with complete covariate data.

RESULTS

There were 193,412 children from 71 centers in 29 countries included in the analyses. In these children, the reported use of antibiotics in the first year of life was associated with a significantly increased risk of current wheeze (OR, 1.95; 95% CI, 1.88-2.03; [Table I](#)). The increased risks of current wheeze associated with antibiotics use in the first year of life were very similar for girls and boys (OR, 1.95; 95% CI, 1.84-2.07; and OR, 1.96; 95% CI, 1.85-2.07, respectively).

There were 103,653 children 6 to 7 years old from 47 centers in 20 countries with complete covariate data enabling them to be included in the further multiple regression analyses. In these children, the association between the reported use of antibiotics in the first year of life and the risk of current wheeze was virtually identical to that in the analysis for all children (OR, 1.96; 95% CI, 1.85-2.07; [Table I](#)). When these analyses were further adjusted for other asthma risk factors listed that had shown associations in univariate analyses, the OR for antibiotic use fell slightly to 1.70 (95% CI, 1.60-1.80; [Table I](#)). Overall, 70.2% of children with current wheeze were reported to have used antibiotics in the first year of life, and the population-attributable risk was 29%. When the effects of antibiotic use and paracetamol use in the first year of life were considered separately (not shown in table), adjusted for other asthma risk factors, antibiotic use (but not paracetamol) in the first year of life had an OR of 1.74 (95% CI, 1.58-1.92), whereas that for paracetamol (but not antibiotics) was 1.41 (95% CI, 1.29-1.54), and the use of both medications had an OR of 2.65 (95% CI, 2.45-2.86).

The increased risk of current wheeze associated with antibiotic use in the first year of life was observed consistently in different regions of the world ([Table II](#); [Fig 1](#)). The 1 exception was Africa (OR, 0.81), but the number of children involved was small, and the 95% CI (0.20-3.20) was broad ([Table II](#)).

The reported use of antibiotics in the first year of life was also associated with a significantly increased risk of severe asthma symptoms (defined as wheezing causing sleep disturbance, or wheezing limiting speech, or 4 or more attacks of wheezing in the past 12 months), and with asthma ever ([Table I](#)). Once again, the OR fell slightly (from 2.12 to 1.82) when the analysis was adjusted for other asthma risk factors.

The reported use of antibiotics in the first year of life was also associated with significantly increased risks of current symptoms of rhinoconjunctivitis and eczema ([Table I](#)). The risks were similar for girls and boys (data not shown) and were observed in all of the 9 different regions of the world ([Table II](#); [Figs 2 and 3](#)).

DISCUSSION

We have investigated the risk of developing symptoms of asthma and other allergic disorders in children 6 and 7 years old associated with the use of antibiotics in the first year of life. We found that the reported use of antibiotics in the first year of life was associated with parental-reported symptoms of asthma in children 6 and 7 years old, after adjustment for other asthma risk factors (including sex, region of the world, language, per capita gross national income, maternal education, breast-feeding, current maternal smoking, current paternal smoking, consumption of vegetables, consumption of pulses, consumption of fruit, paracetamol use in first year of life, current paracetamol use, older siblings, and younger siblings). The association was present in all major regions of the world (with the possible exception of Africa),

TABLE I. Association between antibiotic use in the first year of life and current symptoms of asthma, rhinoconjunctivitis, and eczema in children 6 to 7 years old

	OR (95% CI)		
	Adjusted* (all children)	Adjusted† (children with complete covariate data)	Multivariate analysis‡ (children with complete covariate data)
Current wheeze	1.95 (1.88-2.03)	1.96 (1.85-2.07)	1.70 (1.60-1.80)
Current severe wheeze	2.04 (1.92-2.16)	2.12 (1.96-2.30)	1.82 (1.67-1.98)
Asthma ever	2.13 (2.04-2.23)	2.21 (2.08-2.34)	1.94 (1.83-2.06)
Current symptoms of rhinoconjunctivitis	1.86 (1.78-1.94)	1.80 (1.70-1.92)	1.56 (1.46-1.66)
Current symptoms of eczema	1.60 (1.53-1.67)	1.58 (1.49-1.68)	1.42 (1.33-1.51)

*Adjusted for sex, region of the world, language, and gross national income.

†Adjusted for sex, region of the world, language, and gross national income. Including centers with at least 70% of data for antibiotic use; all children with missing values for antibiotic use or sex were excluded.

‡Multivariate analysis including centers with at least 70% data available for all covariates. All children who had a missing value for any of the covariates have been removed. Adjusted for sex, region of the world, language, gross national income, maternal education, breast-feeding, current maternal smoking, current paternal smoking, consumption of vegetables, consumption of pulses, consumption of fruit, paracetamol use in first year of life, current paracetamol use, older siblings, and younger siblings.

TABLE II. Associations between antibiotic use in the first year of life and current symptoms of asthma, rhinoconjunctivitis, and eczema in children 6 to 7 years old in different regions of the world: multiple regression analyses in children with complete covariate data

Region	Countries (no.)	Centers (no.)	Children (no.)	OR (95% CI)* Asthma (wheeze)	OR (95% CI)* Rhinoconjunctivitis	OR (95% CI)* Eczema
Africa	1	1	890	0.81 (0.20-3.20)	2.06 (0.26-16.61)	1.25 (0.45-3.44)
Asia-Pacific	2	4	10,092	1.79 (1.42-2.26)	1.94 (1.60-2.34)	1.42 (1.20-1.69)
Eastern Mediterranean	2	4	8,237	1.54 (1.24-1.90)	1.52 (1.06-2.18)	1.22 (0.80-1.84)
Indian Subcontinent	1	11	27,020	1.52 (1.23-1.88)	1.34 (1.11-1.62)	1.33 (1.06-1.66)
Latin America	5	6	12,703	1.96 (1.67-2.30)	1.62 (1.37-1.92)	1.65 (1.40-1.95)
North America	2	2	2,656	1.75 (1.42-2.17)	1.22 (0.92-1.63)	1.56 (1.18-2.04)
Northern and Eastern Europe	3	3	6,540	1.72 (1.40-2.12)	1.87 (1.41-2.48)	1.47 (1.17-1.85)
Oceania	1	4	9,206	1.81 (1.58-2.07)	1.64 (1.39-1.94)	1.43 (1.24-1.65)
Western Europe	3	12	26,309	1.57 (1.42-1.74)	1.47 (1.31-1.65)	1.34 (1.21-1.49)

*Multiple regression analysis including centers with at least 70% data available for all covariates. All children who had a missing value for any of the covariates have been removed. Adjusted for sex, region of the world, language, gross national income, maternal education, breast-feeding, current maternal smoking, current paternal smoking, consumption of vegetables, consumption of pulses, consumption of fruit, paracetamol use in first year of life, current paracetamol use, older siblings, and younger siblings.

with an overall prevalence OR of 1.70 (95% CI, 1.60-1.80). Similar associations were observed between the use of antibiotics in the first year of life and the risk of severe asthma symptoms and asthma ever. Weaker (but still statistically significant) associations were also observed for symptoms of rhinoconjunctivitis and eczema.

Before these findings are discussed, the limitations of this study should be considered. The questionnaire was completed by the parents of the children 6 and 7 years old, and information on environmental exposures such as antibiotics use in the first year of life was obtained retrospectively. This could potentially lead to recall bias, particularly if parents of children with asthma were more likely to recall antibiotic use in the first year of life than parents of children without asthma. This is certainly possible, but there is no evidence currently available to assess whether such a bias exists and what its strength (or direction) may be.

Selection bias seems unlikely because the average response rate from centers included in this analysis was 85%. The hypothesis that antibiotics used in infancy may predispose to asthma is not widely known among the general public, and it is therefore unlikely that parents would have overestimated their child's use of antibiotics for this reason.

Further potential sources of bias arise from the necessity to translate the questionnaire into many languages, and inconsistency across the world in the brand names used for antibiotics. To minimize any translation bias, investigators followed a standardized protocol that included back-translation to English.^{25,27} Investigators were instructed to substitute locally appropriate brand names in the antibiotics questions to ensure that the questions were relevant for the local population. Language was also included in the logistic regression models. The consistency of the associations across regions suggests that these potential sources of bias were not significant.

A further limitation is that no information was available on the types of antibiotics used, in particular whether they were broad-spectrum or narrow-spectrum. It might be expected that the latter may not have an appreciable impact on the complex gut microflora, which are made up of more than 500 species, each with numerous different strains.⁷ Thus, it might be expected that any increased risk of asthma and allergies stemming from antibiotic use early in life would be stronger for broad-spectrum antibiotics, and relatively weak for narrow-spectrum antibiotics. In fact, as noted, negative studies have generally included any antibiotic use and/or have involved a relatively broad age range, whereas the positive studies have generally been limited to age less than 2 years and to

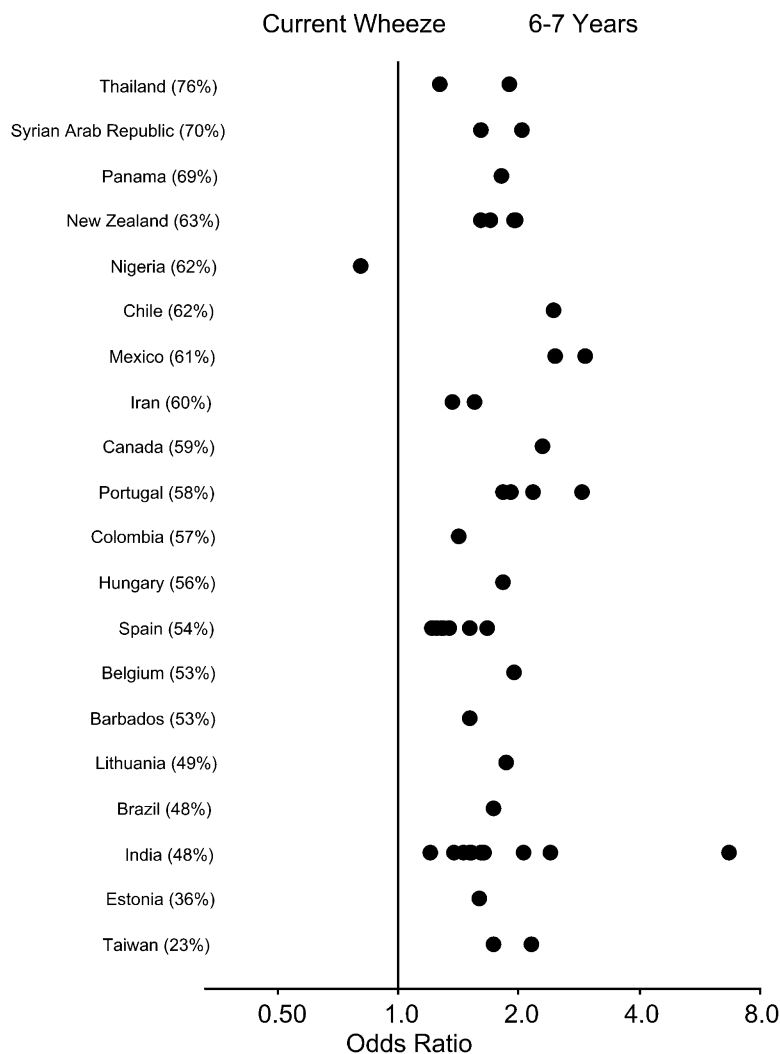


FIG 1. Forest plot showing the adjusted ORs for the associations between the reported use of antibiotics in the first year of life and current asthma symptoms in children 6 to 7 years old from 47 centers in 20 countries. For each country, the percentage of children exposed to antibiotics appears in brackets.

broad-spectrum antibiotics.^{22,23} For example, Voor et al²³ found that antibiotics were a risk factor for asthma symptoms in Estonia but not in Sweden, and related this finding to the practice of prescribing broad-spectrum antibiotics in Estonia, whereas in Sweden mostly penicillin was prescribed. However, the lack of more specific information in the current study on the types of antibiotics used cannot in itself explain the increased risks that were observed, and it is possible that stronger increased risks could have been observed if more specific antibiotic information had been available.

A further limitation of the study is that it would have been useful to have information on atopy because the hygiene hypothesis implies that the association of antibiotic use with asthma symptoms, if it is causal, is likely to be stronger for atopic than for nonatopic asthma.³⁵

Overall, these limitations do not appear to explain the increased risks associated with antibiotic use, which are relatively strong, and relatively consistent across regions with varying environmental and socioeconomic conditions. Furthermore, the study has a number of strengths, including the large numbers of children surveyed, and the fact that many countries with varying

environments and socioeconomic conditions were analyzed with an identical methodology and produced similar findings.

In fact, the findings for antibiotic use in the first year of life are stronger than those previously reported for paracetamol use³² from the same data set—for antibiotic use in the first year of life, the OR was 1.96, compared with 1.77 for paracetamol, and the population-attributable risk for antibiotic use in the first year of life was 29%, compared with 21% for paracetamol.³² Furthermore, the increased risk associated with antibiotic use fell only 27% (from 1.96 to 1.70) when adjusted for other risk factors (including paracetamol use), whereas the corresponding estimate for paracetamol fell by 40% (from 1.77 to 1.46) when adjusted for other risk factors (including antibiotic use).³⁴ This indicates that residual confounding is less likely to be the explanation for the antibiotic findings, whereas it is a more likely explanation for the paracetamol findings. In fact, the findings reported here for antibiotic use are the strongest findings for exposures in the first year of life reported to date from the ISAAC Phase III Environmental Questionnaire data. Furthermore, the findings are highly consistent with those of previous similar studies.²¹

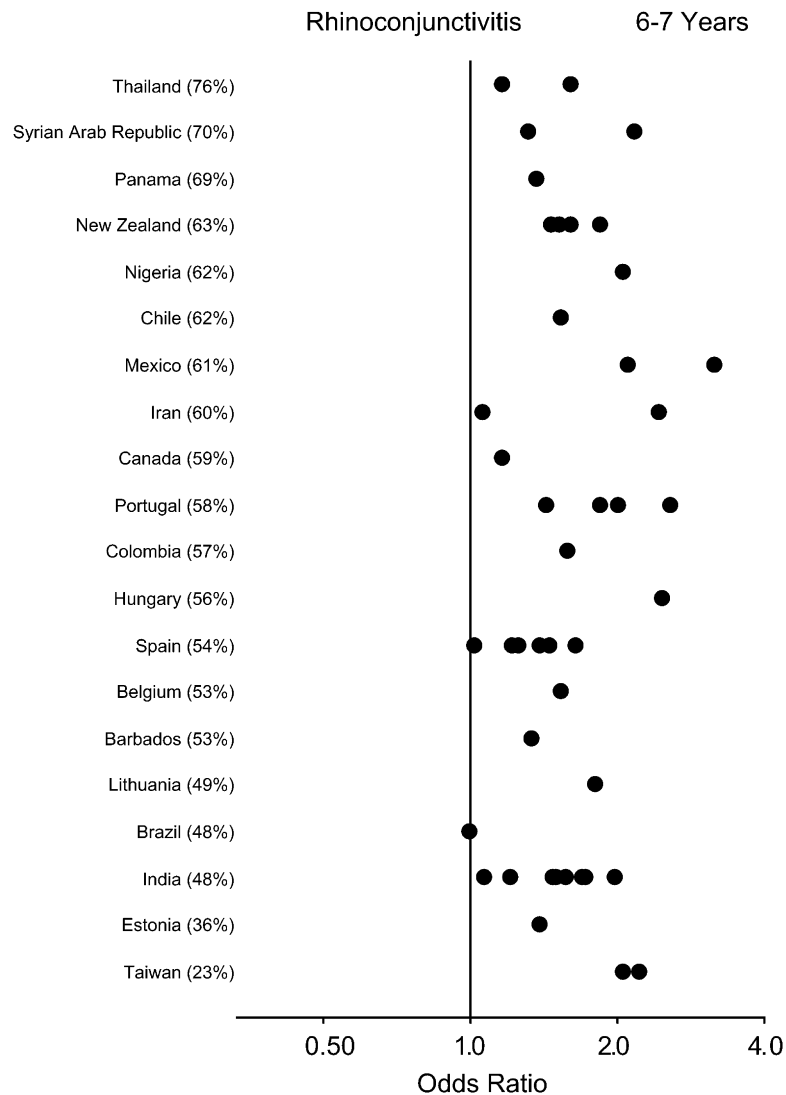


FIG 2. Forest plot showing the adjusted ORs for the associations between the reported use of antibiotics in the first year of life and current symptoms of rhinoconjunctivitis in children 6 to 7 years old from 47 centers in 20 countries. For each country, the percentage of children exposed to antibiotics appears in brackets.

However, although it is clear that an association exists between antibiotic use in the first year of life and subsequent asthma risk, it is by no means clear that this association is causal. In this respect, Kummeling and Thijs³⁶ have discussed 2 possible alternative explanations for such associations: (1) they could be a result of reverse causation, for example if antibiotics were prescribed because of respiratory symptoms; and (2) they could be a result of confounding by indication, for example if antibiotics were prescribed for chest infections, which were in turn associated with subsequent respiratory disease.

This is a cross-sectional study, and it is not possible to assess these 2 possible sources of bias directly. With regard to reverse causation, Kummeling and Thijs³⁶ conclude that this is an unlikely explanation for the association observed in prospective studies because the associations persisted after making sure that antibiotic exposure had preceded the outcomes of interest. On the other hand, they concluded that confounding by indication was a possible explanation for the observed associations, because these reduced markedly when adjusted for chest infections since

birth. A similar pattern has been observed for paracetamol.³⁷ We were not able to assess this possible bias directly in the current study, although we attempted to do so indirectly by adjusting for factors such as paracetamol use, and maternal educational level, which might have been associated (positively or negatively) with chest infections in infancy. When the analyses were adjusted for these potential confounders, the strength of the association between antibiotics use in the first year of life and asthma reduced from 1.96 to 1.70. Thus, the overall association between antibiotic use in the first year of life, and subsequent asthma risk, was in part a result of confounding by other asthma risk factors. However, the confounding was relatively weak (at least for the factors that were included in the model).

In summary, this study, the largest of its type, has confirmed that there is an association between antibiotic use in the first year of life and current symptoms of asthma, rhinoconjunctivitis, and eczema in children 6 to 7 years old, and that this association is present in virtually all regions of the world. Further research is required to determine whether the observed associations are

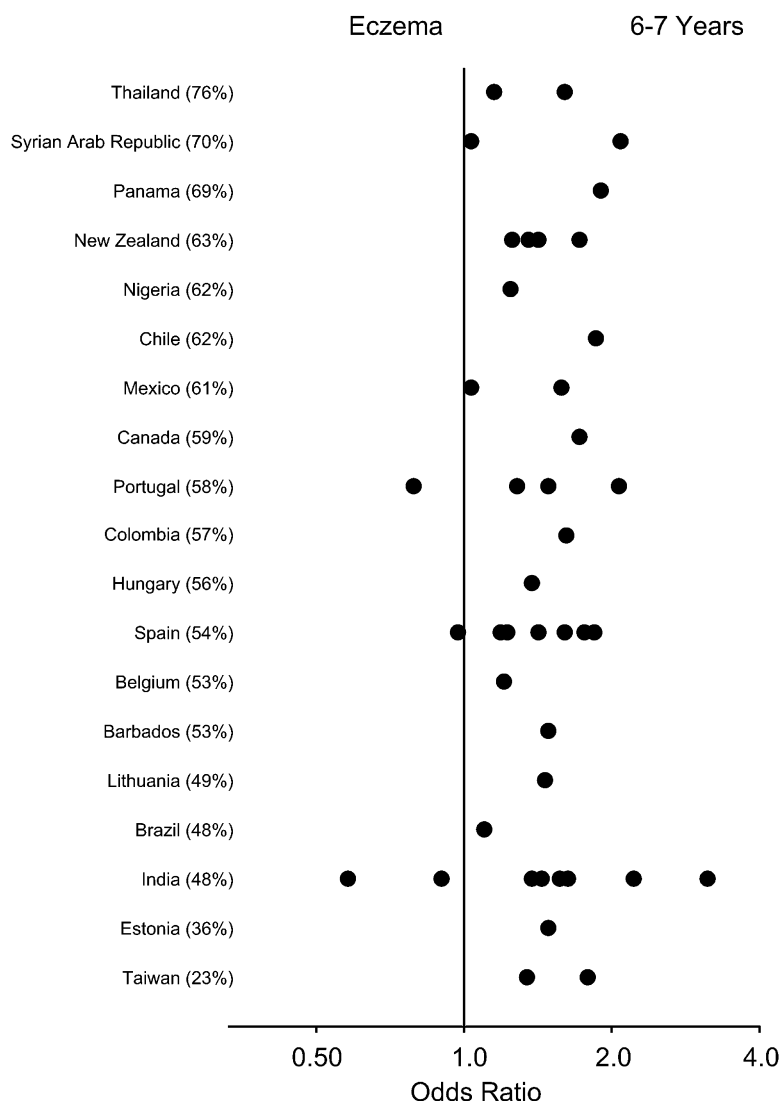


FIG 3. Forest plot showing the adjusted ORs for the associations between the reported use of antibiotics in the first year of life and current symptoms of eczema in children 6 to 7 years old from 47 centers in 20 countries. For each country, the percentage of children exposed to antibiotics appears in brackets.

causal, or are a result of confounding by indication or reverse causation.

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Key messages

- ISAAC Phase III has investigated the association between the use of antibiotics in the first year of life and the subsequent risks of symptoms of asthma, rhinoconjunctivitis, and eczema in 193,412 children from 71 centers in 29 countries.
- Reported use of antibiotics in the first year of life was associated with an increased risk of current asthma symptoms.
- The findings were stronger than those previously reported for paracetamol from the same data set, and the association reduced only slightly when adjusted for other asthma risk factors including paracetamol use.
- Further research is needed to determine whether the observed associations are causal, or are the result of confounding by indication or reverse causation.

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