

Does the use of antibiotics in early childhood increase the risk of asthma and allergic disease?

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Summary

Background One of the mechanisms evoked to explain the increasing prevalences of asthma and allergy, in particular among children, is the 'Western lifestyle' or 'hygiene' hypothesis. As early childhood infections are assumed to hold a protective effect on the development of asthma and allergies, the use of antibiotics at that sensitive age may lead to an increased risk of asthma and allergy.

Objective The aim of this study is to investigate the association between the use of antibiotics in the first year of life and the subsequent development of asthma and allergic disorders.

Methods In a population-based sample of 7-and-8-year-old children questionnaire and skin prick test data were collected from 1206 and 675 subjects, respectively. Prevalence rates of asthma, allergic disorders and skin test positivity were compared between children with and without early life use of antibiotics, taking into account other possible risk factors including early respiratory infections. The effect of genetic predisposition was investigated by stratified analyses of children with and without parental hay fever.

Results The use of antibiotics during the first year of life was significantly associated with asthma (OR = 1.7, 95% CI 1.0–3.1), hay fever (OR = 2.3, 95% CI 1.3–3.8) and eczema (OR = 1.3, 95% CI 1.0–1.8). No significant relationship was found with skin test positivity (OR = 1.1, 95% CI 0.7–1.7). After stratification for the presence of parental hay fever, children without parental hay fever did not show any significant associations between antibiotics use and asthma or allergy, whereas in children with parental hay fever the use of antibiotics was significantly related with asthma (OR = 2.3, 95% CI 1.1–5.1), hay fever (OR = 2.8, 95% CI 1.5–5.1) and eczema (OR = 1.6, 95% CI 1.0–2.6), and of borderline statistical significance with skin test positivity (OR = 1.6, 95% CI 0.9–3.0).

Conclusion Early childhood use of antibiotics is associated with an increased risk of developing asthma and allergic disorders in children who are predisposed to atopic immune responses. These findings support recent immunological understanding of the maturation of the immune system.

Keywords: childhood asthma, allergy, antibiotics, risk factors, Western lifestyle, ISAAC

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Introduction

There is accumulating evidence of an increasing prevalence of asthma and allergic disease over recent decades, particularly in children and young adults in 'developed' countries [1–5]. From many studies worldwide considerable variation

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has been found in asthma and allergy prevalences between countries. These studies mostly used different methodologies with respect to asthma definition, study population and questionnaires. However, also in international multicentre epidemiological surveys using standardized questionnaires, a great variation has been found in the prevalences of asthma and allergy, both in adults (ECRHS) and in children (ISAAC) [6,7].

In order to explain these differences over time as well as geographically, some interesting hypotheses have been proposed. One of the more challenging is the 'Western lifestyle' hypothesis, in which the increase of asthma is associated with certain socio-economic conditions, particularly common in developed western countries [8,9]. One of the effects of this lifestyle is the decreasing prevalence of childhood infections, that are assumed to hold a protective effect for the development of asthma and allergy [10,11].

This decreasing prevalence of early childhood infections can be explained by a lowered risk of exposure to infectious agents in infancy and childhood as a result, among others, increased immunization, improved sanitary conditions and smaller family size [12–15]. Another factor related to this reduced exposure to infectious diseases is the use of antibiotics in early childhood. Two recent studies showed a significant positive association between the use of antibiotics in early life and subsequent development of atopic disorders [16] and a history of asthma and wheeze [17]. However, as commented correctly in both studies, the use of antibiotics may be the consequence of an increased occurrence of respiratory infections in children having an asthmatic or allergic constitution. Because of this reverse causation, caution is needed in interpreting these results.

Recent research has shown that the protective effect of natural infections may be due to their influence on the development of the immune system in early life [18]. Abating exposure to infectious agents may skew the balance between T-cell subpopulations from (normal) Th1-cell responses towards (atopic) Th2-cell responses, including increased production of IgE [19]. Furthermore, a diminished Th1-like immune response in early life may be a marker of an inherited predisposition to allergic disease [20]. Therefore, it is conceivable that the effects of antibiotics in early life occur more particularly in children with a genetic predisposition for an allergy-type of immune response.

In the present study we assessed the association between the use of antibiotics in early childhood and the subsequent development of asthma and allergy in a population-based sample of 7- and 8-year-old schoolchildren. In addition, we examined whether this relationship may be different between children with and without a genetic predisposition to allergic disease.

Materials and methods

Subjects

The study design was based upon the International Study of Asthma and Allergy in Childhood (ISAAC) protocols. ISAAC is an international cross-sectional study on the prevalence and severity of asthma and allergy in children by standardized methodology. Aims and methods of this study have been described previously [21].

The target population consisted of all 6- and 7-year-old children living in urban Antwerp and adjacent residential municipalities. Approximately 130 primary schools were invited to co-operate in the study. After identification of all eligible children from these schools, parents were asked consent for their children to participate in the study.

In phase I a short questionnaire on asthma-like symptoms, rhinitis and eczema was distributed through the schools to be completed by the children's parents. Next, a random sample of 1584 subjects, stratified by gender, was asked through their parents to participate in the second phase of the study. Of these 1193 (75%) responded positively. In addition, in order to enrich this sample with symptomatic subjects, all remaining children with an affirmative answer on the questions on wheeze, asthma or chronic cough in the phase I questionnaire were also invited. The response rate of this second sample was 400/515 (77%). Of all subjects in phase II 1016 agreed to participate in skin prick testing. Questionnaire and skin prick data collection took place between September 1995 and March 1996 (when the children were 7 and 8 years of age). Exclusion of all subjects with insufficient skin prick testing or questionnaire data resulted in a study population of 1592 subjects with a completed questionnaire and 957 subjects with satisfactory skin prick test results.

Questionnaire

Data on demographic and environmental characteristics, respiratory symptoms and use of medication were collected by means of an extended version of the standardized core questionnaire of the ISAAC Study [7]. Asthma was derived from the question 'has your child ever had asthma?'. Allergy symptoms used in the analyses were: 'has your child ever had hay fever?', and 'has your child ever had eczema?'. Questions on use of antibiotics were: 'did your child receive antibiotics in the first year of life?' and 'if so, at what age: 0–3 months, 4–6 months, 7–12 months?'. Lower airway respiratory infection (LRI) was assessed by asking: 'has your child had a severe pulmonary or lower airway respiratory infection in the first two years of life, apart from croup?'

Skin prick testing

Skin prick testing with five common aeroallergens was carried out by standard procedures. The allergens tested were *Dermatophagoides pteronyssinus* (house dust mite, HDM), cat, *Alternaria tenuis* (mold), timothy grass and birch pollen, using histamine chloride and allergen diluent as positive and negative controls, respectively (ALK, Copenhagen, Denmark). Weal diameters were recorded 15 min after application of the antigens. Mean diameters were calculated as the mean of the widest diameter and the perpendicular diameter measured at its midpoint. A mean weal diameter of more than 2 mm was considered a positive response. Responders to the negative control (>1 mm) and nonresponders to the positive control (<3 mm) were excluded from the analyses. Atopy was defined as having one or more positive response (STP, skin test positivity).

Data analyses

To investigate the effects of antibiotics in the first year of life on subsequent asthma morbidity, the use of antibiotics had to precede the occurrence of asthma symptoms. Therefore all children with reported asthma, wheeze or chronic cough within the first year of life were excluded from the analyses.

The use of antibiotics was compared with regard to the outcome variables asthma, hay fever, eczema and atopy. In univariate analyses crude associations between use of antibiotics and outcome variables were investigated using 2×2 tables. To identify potential confounding factors, associations between population characteristics and outcome variables were also investigated using 2×2 tables. Differences between subgroups with and without antibiotics use were tested by Chi-square test.

To assess the independent associations between use of antibiotics and the occurrence of asthma and allergy, multiple logistic regression analysis was used, with adjustment for the effects of potential risk factors. In separate regression analyses each outcome variable acted as dependent variable. All analyses were performed with adjustment for area of residence, gender, parental asthma, parental hay fever, more than two older siblings, maternal smoking during pregnancy and passive smoking during the first 6 months of life. Associations between antibiotics and asthma or allergy symptoms can also be explained as being a consequence of asthma or allergy, due to an increased risk of respiratory infections. To reduce the likelihood of this reverse causation, all regression analyses were additionally adjusted for a history of severe respiratory infections during the first two years of life. Thus, the associations found between use of antibiotics and the prevalence of asthma and allergy outcome variables are independent of the relationship between

asthma or allergy and severe respiratory infections that occurred in the first 2 years of life. Interactions (product terms) between use of antibiotics and early respiratory infections were examined for each outcome variable. None of these interactions were statistically significant and therefore were eliminated from the regression models.

To examine the effect of genetic predisposition on the associations between the use of antibiotics and the outcome variables, the study population was stratified for parental hay fever, defined as having at least one parent with hay fever. Subsequently, odds ratios for use of antibiotics were calculated separately for subjects with and without parental hay fever. Within each stratum children without use of antibiotics acted as referential category.

All tests were two-sided, P -values <0.05 were considered to be statistically significant, as were odds ratios with 95% confidence intervals not including the value 1. Statistical analyses were performed using SPSS 9.0 for Windows (SPSS Inc. Chicago, USA).

The study has been approved by the Ethical Committee of the University of Antwerp. Written informed consent was obtained from the parents of all participating children.

Results

After exclusion of children with asthma or asthma-like symptoms within the first year of life ($n = 300$) and missing data on the key variable (antibiotic use in the first year of life) ($n = 86$), the study population consisted of 1206 children with extended questionnaire data and 675 children with additional data on skin prick tests.

The prevalence of antibiotics use in the first year of life was 31.8% ($n = 384$). Of these, 168 children received antibiotics between 0 and 6 months (13.9%), and 222 children (18.4%) between 7 and 12 months (of 51 children not known).

Population characteristics, stratified by use of antibiotics, are presented in Table 1. The prevalences of asthma, hay fever and eczema were significantly higher in children with use of antibiotics in their first year of life. Also lower airway respiratory infections in early life, parental hay fever, maternal smoking during pregnancy and exposure to smoking during the first 6 months of life were more prevalent in children who received antibiotics during their first year of life. Having more than two older siblings was inversely related with use of antibiotics, whereas parental asthma and being atopic showed no significant difference between children with and without use of antibiotics.

In multiple logistic regression analyses the associations between the use of antibiotics during the first year of life and asthma-and allergy outcome at age 7 and 8 were assessed with adjustment for gender, residential area and the confounding risk factors parental asthma, parental hay fever,

Table 1. Population characteristics (*n*,%) of study population (total *n* = 1206), stratified by use of antibiotics in 1st year of life

Characteristic	Antibiotics (<i>n</i> = 384)		No antibiotics (<i>n</i> = 822)		Crude OR (95% CI)
	<i>n</i> /N	%	<i>n</i> /N	%	
Suburban area	224/384	58.3	488/822	59.4	1.0 (0.7–1.2)
Male gender	206/384	53.6	372/822	45.3	1.4 (1.1–1.8)
Ever asthma	27/384	7.0	28/822	3.4	2.1 (1.3–3.7)
Hay fever	34/380	8.9	33/813	4.1	2.3 (1.4–3.8)
Eczema	85/379	22.4	148/814	18.2	1.3 (1.0–1.8)
Lower respiratory					
Infections (LRI)	56/381	14.7	42/817	5.1	3.2 (2.1–4.8)
>= 2 older sib	76/381	19.9	216/820	26.3	0.7 (0.5–0.9)
Parental asthma	38/382	9.9	75/819	9.2	1.1 (0.7–1.7)
Parental hay fever	166/381	43.6	276/818	33.7	1.5 (1.2–1.9)
Parental eczema	83/380	21.8	133/810	16.4	1.4 (1.0–1.9)
Mother smoking					
in pregnancy	66/381	17.3	108/817	13.2	1.4 (1.0–1.9)
Exp smoke <6m*	111/382	29.1	184/819	22.5	1.4 (1.1–1.9)
Atopy† (<i>n</i> = 675)	45/217	20.7	85/458	18.6	1.1 (0.8–1.7)

*Exposure to smoke in first 6 months of life, †atopy as skin test positivity.

Table 2. Association of antibiotics use in 1st year with asthma and allergy outcome variables; odds ratios (95% CI) of use of antibiotics in first year, adjusted for area, gender, parental asthma, parental hay fever, >= 2 older siblings, maternal smoking in pregnancy, exposure to smoke in first 6 months and LRI in infancy

	N*	Asthma (<i>n</i> = 53)	Hay fever (<i>n</i> = 66)	Eczema (<i>n</i> = 230)	N*	Atopy (<i>n</i> = 130)
No antibiotics	805	1	1	1	450	1
Antibiotics 1st year	375	1.7 (1.0–3.1)	2.3 (1.3–3.8)	1.3 (1.0–1.8)	210	1.1 (0.7–1.7)

*Number of subjects in each antibiotics subgroup (atopic diseases and atopy, respectively).

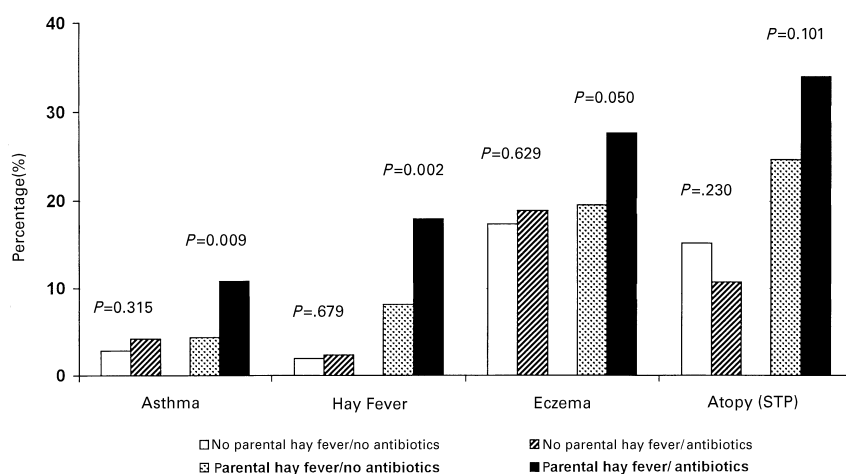
**Fig. 1.** Prevalence of outcome variables asthma and allergy stratified for parental hay fever and antibiotics use in 1st year of life. *P*-values for differences in outcome variables between subjects with and without use of antibiotics.

Table 3. Association of antibiotics use in 1st year with asthma and allergy outcome variables, stratified for parental hay fever. Odds ratios (95% CI) of use of antibiotics in first year adjusted for area, gender, parental asthma, >2 older siblings, maternal smoking in pregnancy, exposure to smoke in first 6 months and LRI in infancy

	N*	Asthma (n = 53)	Hay fever (n = 66)	Eczema (n = 230)	N*	Atopy (n = 130)
No parental hay fever						
No antibiotics	531	1	1	1	285	1
Antibiotics 1st year	211	1.2 (0.5–2.9)	1.1 (0.4–3.5)	1.2 (0.8–1.9)	118	0.7 (0.4–1.4)
Parental hay fever						
No antibiotics	274	1	1	1	165	1
Antibiotics 1st year	164	2.3 (1.1–5.1)	2.8 (1.5–5.1)	1.6 (1.0–2.6)	92	1.6 (0.9–3.0)

*Number of subjects in each antibiotics subgroup (atopic diseases and atopy, respectively).

older siblings, maternal smoking during pregnancy, exposure to smoke during the first 6 months of life and a history of lower airway respiratory infections during the first 2 years of life (Table 2). Use of antibiotics was associated with an increased risk of ever asthma (OR 1.7, 95% CI 1.0–3.1), hay fever (OR 2.3, 95% CI 1.3–3.8), and eczema (OR 1.3, 95% CI 1.0–1.8). No significant association was found with atopy (OR 1.1, 95% CI 0.7–1.7).

The prevalence of the outcome variables in relation to use of antibiotics in the first year of life, after stratification for the presence of parental hay fever, is shown in Fig. 1. In children without parental hay fever ($n = 757$) no significant differences in prevalence of asthma and allergic disease existed between children with and without use of antibiotics in the first year of life. In contrast, among children with a parent with hay fever ($n = 442$) prevalence rates of asthma, hay fever and eczema were significantly higher in those who received antibiotics in their first year of life. In multivariate analyses (Table 3) the use of antibiotics was significantly associated with asthma in children with parental hay fever (OR 2.3, 95% CI 1.1–5.1), whereas in children without a parent with hay fever only a weak and nonsignificant relationship existed between asthma and use of antibiotics (OR 1.2, 95% CI 0.5–2.9). Similar results were obtained regarding hay fever and eczema. In the association between antibiotics and atopy the effect modification by parental hay fever appeared to be even more pronounced: an odds ratio of 0.7 (0.4–1.4) in children without a parent with hay fever, compared with an odds ratio of 1.6 (0.9–3.0) in children with parental hay fever.

Discussion

This cross-sectional study among 7- and 8-year-old school children showed that children who received antibiotics during their first year of life have an increased risk of developing subsequent asthma and allergic diseases, as

compared to children who did not receive antibiotics. However, this increased risk is confined to children with a genetic predisposition to allergic disease. Moreover, the association between antibiotics use and skin test positivity (as objective marker of atopy) in particular is strongly determined by this genetic predisposition.

Our results correspond in part with the findings of the two studies published until now on this subject. Farooqi *et al.* [16] found a significant association (odds ratio 2.1) between antibiotics and atopic diseases (asthma, hay fever or eczema). However, this study examined a population from a different age group (12–20 years of age) and presented only one adjusted odds ratio for all three atopic disorders together. Wickens *et al.* [17] reported an adjusted odds ratio for asthma of 2.74 with antibiotics used ever and of 4.05 with antibiotics used during the first year of life. These results originated from a specific population of children attending Steiner schools in New Zealand, an anthroposophic population that would differ from average Western lifestyle, including a limited use of antibiotics. However, their proportion of 36% of children receiving antibiotics during the first year of life was even higher than in our study population. The former and current epidemiological studies, conducted in three different study populations, thus found similar associations between the use of antibiotics in early childhood and the development of asthma.

In the two former studies the outcome variables asthma and allergic disorders were defined by patient record data from general practitioners and questionnaire data, respectively. In addition, we also examined skin prick test positivity as a more objective measure for atopy. Without accounting for genetic predisposition, having one or more positive skin test appeared to be unrelated to the use of antibiotics in the first year of life. This finding agrees with Alm *et al.* who conducted a study on anthroposophic lifestyle factors, including use of antibiotics, and atopy in children visiting two Rudolf Steiner schools in Sweden

[22]. They also found a weak and statistically nonsignificant association with atopy, defined by skin prick and blood tests. However, our results show that this association is modified by the child's predisposition to allergy.

In our study skin tests were performed only in a subgroup of children. Although the prevalence of asthma and allergic disorders were lower in this subgroup, no difference was found in the relationship between use of antibiotics and the other outcome variables with children who did not undergo skin prick testing.

The findings of our study may enhance the 'hygiene hypothesis' in which a protective effect of early childhood infections is assumed. Less exposure to infectious agents may result in an unbalance between T-cell subsets through a bias from (normal) Th1-cell responses towards (atopic) Th2-cell responses, including persistent production of IgE [19]. It is recognized that children with a family history of allergies have a diminished ability for secretion of Th1-like cytokines [23]. In an immunological study Prescott *et al.* showed that suppression of Th2 responses in the first year of life was seen in nonatopic children only, whereas in atopic children Th2 responses remained predominant, accompanied by a decreased ability of Th1 responses [24]. Our results support the conclusion from that serological study, suggesting that the initial immune responses to environmental allergens in early childhood occur within an immature T-cell system, as a result of which intracellular exposure to bacteria and viruses are beneficial, or even essential, for a normal maturation of the immune system. However, a restriction has to be made concerning the validity of this hypothesis. Our results suggest that the use of antibiotics in early childhood may affect the immune system in the presence of a genetically determined tendency towards atopic (Th2-like) responses. In genetically predisposed children atopic disease may manifest itself as a result of exposure to allergens by which the immune system is primed for Th2 responses. Early childhood exposure to other environmental factors, such as infectious agents, may prevent this priming mechanism through a switch of the immune system towards normal Th1 responses.

However, given the assumption that virtually all infants start with a Th2-skewed system [25], it remains unclear why, among children without a genetic predisposition for atopy, no effect was seen of the use of antibiotics in infancy on the development of asthma and atopy. As the prevalence of asthma and allergic disease was low among these children, their immune system must have developed into a nonatopic Th1-polarized direction. This may be explained by the probability that a much lower level of exposure to infectious agents will be necessary for the deviation of the immune system, as a result of which antibiotics will not be able to interfere with this process. However, it seems likely that the switch to a predominantly Th1-like phenotype may

also be influenced by other, genetical or environmental, factors. Moreover, the postnatal maturation of the immune system may not solely be a matter of Th1-or Th2-polarization.

As mentioned by Wickens *et al.* [17], antibiotic treatment reduces the intensity and duration of bacterial infections, whereas antibiotics are prescribed mostly for viral infections. Therefore, the increased risk of asthma and allergy could not be explained by a decreased exposure to infections. However, it is conceivable that use of antibiotics during viral infection may prevent secondary bacterial infection. An alternative explanation may be found in the influence of antibiotics in early life on the maturation of the immune system through its direct effects on the intestinal microflora [26]. Björkstén *et al.* found differences in intestinal microflora between allergic and nonallergic 2-year-old children [27]. A recent study by Matricardi *et al.* showed that atopy was inversely related to orofaecally transmitted infections only, and not to (viral) infections transmitted otherwise [28].

The overall weaker associations with eczema may be explained by the greater probability of misclassification in the assessment of this outcome variable. In a prospective study on the natural history of asthma by Sporik and colleagues [29] infantile eczema appeared not to be useful as a predictor of atopy as many nonatopic children were affected as well.

The relationship between use of antibiotics in early childhood and the development of asthma and allergy is ambiguous, since the use of antibiotics may only be the representation of an increased risk on respiratory infections in children with an asthmatic or allergic constitution. The studies by Farooqi and Wickes took account, though in different ways, of the sequence of antibiotics use and the occurrence of asthma and allergy. We also controlled for this sequential issue by excluding all children who may have had asthma during or before the use of antibiotics. However, this adjustment may not be sufficient because of inevitable misclassification in the definition and onset of asthma and use of antibiotics. Therefore, we additionally controlled for a history of respiratory infections in early childhood. Consequently, the associations between the use of antibiotics and asthma and allergy are independent of the effect of respiratory infections.

In conclusion, this cross-sectional study shows that children who received antibiotics in their first year of life are at risk of subsequent development of asthma and allergic diseases. However, this increased risk manifests itself only in children who are genetically predisposed to atopic immune responses. These findings support in part recent immunological knowledge on the maturation processes of the immune system. In order to obtain a better understanding of the mechanisms involved in the associations between

early childhood infections and the subsequent development of asthma and allergy and the role of genetic factors in these processes, prospective studies should be conducted in populations with different 'risk levels' of asthma and allergic disorders.

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