

ORIGINAL ARTICLE

Antibiotic use in early life and development of allergic diseases: respiratory infection as the explanation

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Summary

Background Early antibiotic use has been postulated to increase the development of allergic disease. Antibiotic use results from infection. Early infection may play a confounding role in the relationship between antibiotic use and allergic disease.

Objective We aimed to investigate the relationship between antibiotic use during the first year of life and the development of allergic diseases in a birth cohort study, and also to carefully address the confounding effect of early respiratory infection.

Methods Three thousand three hundred and six children were included in this study who participated in investigations at all occasions of 2 months, 1, 4 and 8 years of age. Data on antibiotic use and respiratory infections were collected at the age of 1 year. Diagnoses of allergic diseases at 4 and 8 years of age were derived from the follow-up questionnaires.

Results During the first year of life, 43% ($n = 1420$) of the children received antibiotics and 32% ($n = 1046$) of the children had at least one type of respiratory infection among pneumonia, bronchitis and otitis. In univariate logistic regression analysis and after adjustment for early life factors, antibiotic use during the first year of life was associated with wheeze, asthma, eczema and food hypersensitivity at 4 years of age. After adjustment for the above respiratory infections during the first year of life, only the associations with wheeze and asthma at age 4 years remained statistically significant. These associations became non-significant in a subgroup analysis in children without early allergic signs. At age 8 years, antibiotic use during the first year of life was significantly associated with wheeze and eczema after adjustment for early life factors. The significant associations at age 8 years faded away following further adjustment for the respiratory infections.

Conclusion Our study indicated that the association between early antibiotic use and later allergic disease could at least partially be explained by early respiratory infection.

Keywords allergy, antibiotics, birth cohort study, confounding factors and respiratory infection

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Introduction

Early antibiotic use has been postulated to increase the development of allergic disease due to its disturbance on intestinal microflora and the subsequent influence on the developing immune system towards T-helper 2 immune responses [1, 2]. Studies that show a positive association between antibiotic use and asthma are mostly cross-sectional and retrospective in nature [3–11]. The relation between early antibiotic use and development of allergy

has also been evaluated in prospective studies. Most of the prospective studies show a null association between antibiotic use in early life and later allergic disease [12–16]. The follow-up duration of these prospective studies is usually short, which is difficult to address the effect of early antibiotic use on the full development of allergic disease. Allergic outcomes such as wheeze, asthma and eczema have been the main focus in previous prospective studies, but other allergic outcomes are overlooked, such as sensitization and food hypersensitivity.

In addition, early antibiotic use results from early infection [17, 18]. Although controversial, respiratory infection in early life, in particular lower respiratory tract infection has been demonstrated to increase the risk for the development of allergic disease [19–22]. When the confounding effect of early respiratory infection on the relationship between antibiotic use and development of allergic disease was investigated in previous studies, early respiratory infection was normally adjusted among other early life factors. Thus, the individual confounding effect of early respiratory infection is not readily observed. Recent, prospective studies have attempted to show the individual confounding effect of early respiratory infection, but more convincing evidence is needed [13, 16].

A good understanding of the relationship between antibiotic use and allergic disease is essential for clinicians and health policymakers. Thus, we aimed to investigate the relationship between antibiotic use during the first year of life and the development of allergic disease in a birth cohort study Barn (Children) Allergy Milieu Stockholm Epidemiology (BAMSE), and also to carefully address the individual confounding effect of early respiratory infection. The birth cohort study BAMSE provided us a very good opportunity to further clarify the relationships in a large and long-term followed population.

Methods

We used data from a population-based birth cohort consisting of 4089 infants (2065 boys and 2024 girls) born between 1994 and 1996 in Stockholm, Sweden. Enrolment procedure and inclusion criteria have been described in detail elsewhere [23]. Children were recruited at an average age of 2 months old and followed up at 1 year, 2, 4 and 8 years of age. Questions concerning early antibiotic use and early respiratory infections were answered by parents when the children were at 1 year of age. Diagnoses of allergic diseases at 4 and 8 years of age were derived from the follow-up questionnaires. The study population included 3306 children (81% of the birth cohort), who participated at all occasions of 2 months, 1 year, 4 and 8 years of age (Fig. 1). Information on antibiotic use during the first year of life was available for all these 3306 children. These 3306 children did not differ from the total birth cohort of 4089 children in sex or other demographic factors. Antibiotic use or prevalence of allergic disease such as wheeze, asthma or eczema during the first year did not differ between these 3306 children and the 3925 children who participated at the 1-year follow-up (data not shown). There was one question regarding antibiotic use and four questions regarding respiratory infections in the questionnaire, i.e. Has your child ever received antibiotics, e.g. penicillin (yes/no)? Has your child ever been diagnosed with pneumonia by a doctor (yes/no)? Has your

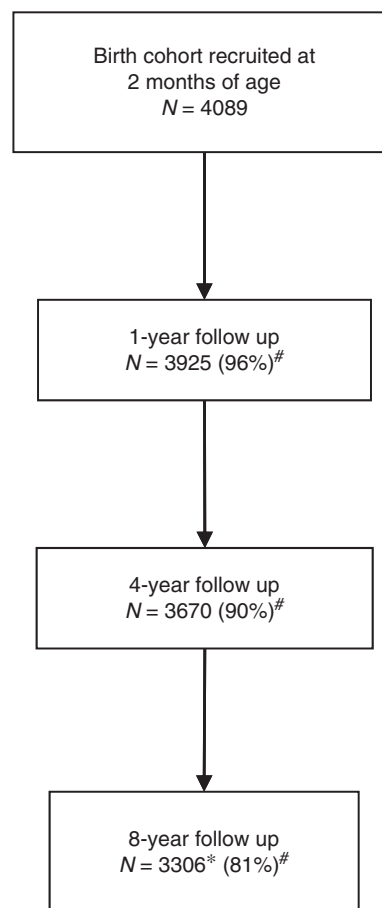


Fig. 1. Flow chart of children who participated in investigations at 2 months, 1, 4 and 8 years of age in the Barn (Children) Allergy Milieu Stockholm Epidemiology birth cohort study. #Follow-up rate compared with the total birth cohort of 4089 children; *number of children who participated at all mentioned occasions.

child ever been diagnosed with bronchitis by a doctor (yes/no)? Has your child had otitis that was treated with antibiotics, e.g. penicillin (yes/no)? and has your child had otitis that was not treated with antibiotics (yes/no)? Otitis in this study was the affirmative answer to either of the last two questions. Courses of antibiotic use were also recorded in the questionnaire.

Questions in the BAMSE questionnaire were derived from the International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire and similar to those applied in other European birth cohort studies [24, 25]. Diagnosis of allergic diseases at 4 or 8 years of age was slightly modified from the ISAAC studies. Wheeze was defined as at least one episode of wheezing in the last 12 months. Asthma was defined as more than three episodes of wheeze or at least one episode of wheeze combined with inhaled glucocorticoids for asthma or asthma symptoms in the previous 12 months [26–28]. Allergic rhinitis (AR) was defined as a runny or blocked nose without concomitant symptoms of having a cold in the previous

12 months according to the ISAAC criteria [24, 26, 28]. Eczema at age 4 was defined as dry skin and itchy rash continuously for at least 2 weeks in the previous 12 months with a typical distribution (face, outer limbs, folds of elbows/wrists, behind the knees, or fronts of ankles) and/or doctor's diagnosis of eczema after 2 years of age [26, 28]. Eczema at age 8 was defined as dry skin and itchy rash continuously for at least 2 weeks in the previous 12 months with a typical distribution (face, folds of elbows/wrists, behind the knees or fronts of ankles) and/or doctor's diagnosis of eczema after 4 years of age. Food hypersensitivity at age 4 was defined as an affirmative answer to the question 'Has your child ever had symptoms to food or drinks after 2 years of age?' plus at least one specific symptoms (gastro-intestinal symptoms, rash, urticaria, swelling lips/eyes, itchy eyes/nose and wheeze) to a specific food item (milk/milk product, egg, fish, nuts, peanut, pea, soy, wheat, stone fruits, lemon, chocolate and banana). Food hypersensitivity at age 8 was defined in a similar way after 4 years of age [29].

Sensitization to airborne allergens was analysed with Phadiatop[®] [a mixture of common inhalant allergens: birch pollen, timothy grass pollen, mugwort pollen, cat, dog, horse, mould (*Cladosporium herbarum*) and house dust mite (*Dermatophagoides pteronyssinus*)], ImmunoCAP[™], Phadia AB, Uppsala, Sweden. Sensitization to food allergens was analysed with fx5[®] (a mixture of food allergens: egg, milk, fish, peanut, wheat and soy), ImmunoCAP[™], Phadia AB. IgE-antibody levels ≥ 0.35 kU_A/L were considered as positive Phadiatop[®] or positive fx5[®]. Any sensitization at 4 or 8 years of age was defined as positive Phadiatop[®] and/or positive fx5[®] [29]. Information on any sensitization was available in 2416 children at 4 years and in 2375 children at 8 years of age among the 3306 children.

Data on other possible risk factors in early life, such as young maternal age, older sibling, maternal smoking habit and parental allergy were collected from the first parent-answered questionnaires when the children were 2 months old. Young maternal age was denoted as the mother's age below 25 years of age at birth of the child. Older sibling was defined as any older siblings in the household. Maternal smoking was defined as the mother smoking at least one cigarette per day at any point of time during pregnancy and/or at the time when her child was 2 months old. Parental allergy was defined as mother and/or father with doctor's diagnosis of asthma and asthma medication and/or doctor's diagnosis of hayfever in combination with furred pets- and/or pollen allergy at the time when their child was 2 months of age [30]. These early life factors were categorized as dichotomous variables (yes vs. no). Information on exclusive breastfeeding was recorded the children were 1 year old. Exclusive breastfeeding denotes that infants were given only breast milk and no formula, cow's milk or solid foods had been

introduced. Exclusive breastfeeding was categorized as ≥ 4 months and < 4 months [30].

Statistical analyses

The relationships between antibiotic use during the first year of life and various allergic diseases at 4 or 8 years of age were evaluated. Allergic diseases included wheeze, asthma, AR, eczema, food hypersensitivity and any sensitization. The risk of antibiotic use during the first year of life was evaluated by logistic regression analysis and presented as odds ratio (OR) and its 95% confidence interval (CI). In the univariate model, crude risk was estimated (Tables 2 and 4 for 4 and 8 years of age, respectively). In the first multivariate model, the risk was adjusted for early life factors (sex, young maternal age, older sibling, maternal smoking, parental allergy and exclusive breastfeeding) (Tables 2 and 4). In the second multivariate model, pneumonia, bronchitis and otitis during the first year of life were additionally included altogether to clarify the confounding effect of respiratory infection (Tables 3 and 5 for 4 and 8 years of age, respectively). The percentage drop of estimated coefficient of antibiotic use between the two multivariate models was calculated as the difference in coefficients divided by the coefficient in the first multivariate model. Dose-response effect of antibiotic use and the corresponding effect following adjustment for the early life factors and respiratory infections were also evaluated (Table 6). To distinguish between IgE-mediated and non-IgE-mediated disease, each outcome was classified into four subgroups according to the status of any sensitization, i.e. no symptoms+no sensitization (reference), no symptoms+sensitization, symptoms+no sensitization (non-IgE-mediated disease) and symptoms+sensitization (IgE-mediated disease). The Wald test was used to assess the interaction between antibiotic use and any respiratory infection (any of pneumonia, bronchitis or otitis), and *P*-values for interaction after adjustment for the early life factors are presented in text. All statistical analyses were performed with STATA 10.0 (College Station, TX, USA). Ethical approval was obtained from the Ethics Committee of Karolinska Institutet, Stockholm, and informed consent was obtained from the parents.

Results

Among the 3306 children included, 1420 (43%) children received antibiotics during the first year of life, among whom 813 (57%) children had one course and the rest had two or more courses of antibiotics. In total, 1046 (32%) children had at least one type of respiratory infection among pneumonia, bronchitis and otitis during the first year of life. Prevalence of allergic outcomes at 4 and 8 years of age among the 3306 children is presented in

Table 1. The prevalence of asthma and food hypersensitivity remained stable between 4 and 8 years of age. There was an increase in the prevalence of AR and sensitization, and a decrease in wheeze and eczema at 8 years of age.

Antibiotic use during the first year of life was associated with allergic diseases at 4 years of age, such as wheeze, asthma, AR, eczema and food hypersensitivity in univariate logistic regression analyses, with crude ORs ranging from 1.2–1.7 (Table 2). After adjustment for early life factors (sex, young maternal age, older sibling, maternal smoking, parental allergy and exclusive breastfeeding), the risks of antibiotic use remained (Table 2). When pneumonia, bronchitis and otitis during the first year of life were additionally added to the above multivariate model, the effects of antibiotic use on allergic diseases diminished, although the association was still significant for wheeze and asthma (Table 3). The percentage drop of estimated coefficients of antibiotic use for allergic diseases at 4 years was 38–98% between the two multivariate models (wheeze 58%, asthma 38%, AR 49%, eczema 98% and food hypersensitivity 50%). Meanwhile, bronchitis during the first year of life was associated with an increased risk of wheeze and asthma at 4 years of age, and otitis was associated with eczema (Table 3).

Antibiotic use during the first year of life was also associated with an increased risk for allergic diseases at 8 years of age in the univariate logistic regression analysis (Table 4). After adjustment for the early life factors, the risk of antibiotic use remained for wheeze and eczema at 8 years of age (Table 4). When pneumonia, bronchitis and otitis were additionally added into the model, the association with wheeze and eczema became non-significant (Table 5), and the percentage drop of coefficient was 49% and 60%, respectively, for wheeze and eczema at 8 years of age. At the same time, bronchitis during the first year of life was associated with an increased risk for wheeze, and otitis was associated with an increased risk for eczema at 8 years of age (Table 5).

There was no interaction between antibiotic use and any respiratory infection (any of pneumonia, bronchitis or

Table 2. Relationship between antibiotic use during the first year of life and development of allergic diseases at 4 years of age

	Antibiotic use during the first year					
	No (<i>n</i> = 1886)			Yes (<i>n</i> = 1420)		
	<i>n</i>	%	OR	<i>n</i>	%	Crude OR (95% CI) Adjusted OR (95% CI)
Wheeze	228	12	1.0	254	18	1.6 (1.3–1.9) 1.4 (1.2–1.8)
Asthma	103	5	1.0	125	9	1.7 (1.3–2.2) 1.5 (1.1–2.0)
Allergic rhinitis	193	10	1.0	176	13	1.2 (1.0–1.5) 1.2 (0.9–1.5)
Eczema	345	18	1.0	318	22	1.3 (1.1–1.5) 1.3 (1.1–1.5)
Food hypersensitivity	173	10	1.0	181	14	1.4 (1.2–1.8) 1.4 (1.1–1.7)
Any sensitization*	335	24	1.0	244	24	1.0 (0.8–1.2) 0.9 (0.7–1.1)

*Any sensitization is defined as a positive Phadiatop[®] and/or fx5[®], i.e. IgE-antibodies >0.35 kU_A/L to common inhalant and/or food allergens. Information on any sensitization at 4 years of age was available in 2416 children. Adjusted OR: after adjustment for sex, young maternal age, older sibling, maternal smoking, parental allergy and exclusive breastfeeding.

otitis) on wheeze ($P=0.46$ for 4 years and $P=0.21$ for 8 years), asthma ($P=0.21$ for 4 years and $P=0.24$ for 8 years), AR ($P=0.54$ for 4 years and $P=0.91$ for 8 years), eczema ($P=0.30$ for 4 years and $P=0.49$ for 8 years) or food hypersensitivity ($P=0.44$ for 4 years and $P=0.08$ for 8 years) after adjustment for early life factors.

Antibiotic use during the first year of life was not associated with any sensitization to airborne and/or food allergens in the univariate analysis (Tables 2 and 4). After adjustment for the early life factors and respiratory infections, neither antibiotic use nor pneumonia, bronchitis or otitis during the first year increased the risk for any sensitization at 4 or 8 years of age (Tables 3 and 5). Similar results were obtained when sensitization to airborne and food allergens were investigated separately (data not shown). To distinguish between IgE-mediated and non-IgE-mediated disease, wheeze, asthma, AR, eczema and food hypersensitivity were classified into subgroups according to the status of any sensitization. In the multivariate analysis including adjustment for early life factors as well as pneumonia, bronchitis and otitis, antibiotic use during the first year of life was associated with an increased risk for non-IgE-mediated wheeze (OR = 1.6, 95% CI 1.1–2.2), asthma (OR = 1.9, 95% CI 1.1–3.1) and food hypersensitivity (OR = 1.6, 95% CI 1.0–2.5) at age 4 years, but not at 8 years of age (data not shown). However, we observed no significant associations with IgE-mediated wheeze, asthma or food hypersensitivity at 4 or 8 years of age (OR = 1.0, 95% CI 0.6–1.7 for wheeze, OR = 1.2, 95% CI 0.6–2.2 for asthma and OR = 1.0, 95% CI 0.6–1.6 for food hypersensitivity at 4 years of age). We observed no significant associations with IgE-mediated or non-IgE-mediated AR or eczema (data not shown).

Table 1. Prevalence of allergic outcomes at 4 and 8 years of age in the 3306 included children

Allergic outcomes	4 years (%)	8 years (%)	<i>P</i> -value*
Wheeze	15	10	<0.001
Asthma	7	6	NS
Allergic rhinitis	11	14	<0.01
Eczema	20	16	<0.001
Food hypersensitivity	12	13	NS
Any sensitization [†]	24	35	<0.001

* χ^2 tests.

[†]Any sensitization is defined as a positive Phadiatop[®] and/or fx5[®], i.e. IgE-antibodies >0.35 kU_A/L to common inhalant and/or food allergens. NS, non-significant.

Table 3. Confounding effect of respiratory infection on the relationship between antibiotic use during the first year of life and development of allergic diseases at 4 years of age (adjusted OR and 95% CI)

During first year of life	Wheeze	Asthma	Allergic rhinitis	Eczema	Food hypersensitivity	Any sensitization
Antibiotic use	1.2 (1.1–1.5)	1.4 (1.1–1.7)	1.0 (0.9–1.3)	1.0 (0.9–1.2)	1.1 (0.9–1.4)	0.9 (0.8–1.1)
Pneumonia	1.0 (0.6–1.7)	1.5 (0.8–2.8)	1.0 (0.5–1.9)	1.4 (0.9–2.2)	1.1 (0.6–2.0)	0.7 (0.3–1.2)
Bronchitis	1.9 (1.4–2.6)	1.7 (1.1–2.7)	1.4 (0.9–2.1)	0.9 (0.7–1.3)	1.4 (0.9–2.1)	1.1 (0.8–1.6)
Otitis	1.1 (0.8–1.4)	0.9 (0.6–1.3)	1.1 (0.8–1.5)	1.4 (1.1–1.8)	1.2 (0.9–1.6)	1.1 (0.8–1.5)

Each multivariate logistic regression model consists of antibiotic use during the first year of life, pneumonia, bronchitis and otitis during the first year of life, sex, young maternal age, older sibling, maternal smoking, parental allergy and exclusive breastfeeding.

Table 4. Relationship between antibiotic use during the first year of life and development of allergic diseases at 8 years of age

	Antibiotic use during the first year					
	No (<i>n</i> = 1886)			Yes (<i>n</i> = 1420)		
	<i>n</i>	%	OR	<i>n</i>	%	Crude OR (95% CI) / Adjusted OR (95% CI)
Wheeze	160	9	1.0	170	12	1.5 (1.2–1.9) / 1.4 (1.1–1.7)
Asthma	106	6	1.0	104	7	1.3 (1.0–1.8) / 1.2 (0.9–1.6)
Allergic rhinitis	245	13	1.0	202	14	1.1 (0.9–1.4) / 1.1 (0.9–1.3)
Eczema	268	15	1.0	255	18	1.3 (1.1–1.6) / 1.3 (1.1–1.6)
Food hypersensitivity	230	12	1.0	206	15	1.2 (1.0–1.5) / 1.2 (0.9–1.4)
Any sensitization*	470	34	1.0	358	36	1.1 (0.9–1.2) / 1.0 (0.8–1.2)

*Any sensitization is defined as a positive Phadiatop[®] and/or fx5[®], i.e. IgE-antibodies >0.35 kU_A/L to common inhalant and/or food allergens. Information on any sensitization at 8 years of age was available in 2375 children. Adjusted OR: after adjustment for sex, young maternal age, older sibling, maternal smoking, parental allergy and exclusive breastfeeding.

Antibiotic use was closely associated with wheeze, asthma and eczema during the first year of life in our study ($P < 0.001$ for all). To exclude a reverse causation, we further evaluated the effect of antibiotic use during the first year of life on wheeze and asthma at 4 years in a subgroup of children without wheeze, asthma or eczema during the first year of life. In this subgroup of children ($n = 2424$), we observed no significant effect of antibiotic use on wheeze and asthma at 4 years of age after adjustment for the early life factors and respiratory infections (OR = 1.2, 95% CI 0.9–1.5 for wheeze and OR = 1.2, 95% CI 0.8–1.7 for asthma).

We also evaluated the dose–response effect of antibiotic use (Table 6). After adjustment for the early life factors and respiratory infections, two courses or more of antibiotic use were significantly associated with wheeze and asthma at 4 years of age (OR, 95% CI, p for trend: 1.6, 1.1–2.2, $P < 0.01$ for wheeze; 1.9, 1.2–3.0, $P < 0.01$ for asthma), but not at 8 years of age. However, when these analyses were performed in the subgroup of children without wheeze, asthma or eczema during the first year

of life, no significant associations with wheeze and asthma at 4 years were observed (OR, 95% CI, p for trend: 1.4, 0.9–2.3, $P = 0.17$ for wheeze; 1.3, 0.6–2.9, $P = 0.45$ for asthma).

Discussion

In our birth cohort study, we found significant associations between antibiotic use during the first year of life and allergic outcomes at 4 years of age in the univariate logistic regression analysis and after adjustment for early life factors. After adjustment for respiratory infections during the first year of life, only the associations with wheeze and asthma at 4 years of age remained statistically significant. However, these associations became non-significant in a subgroup analysis in children without allergic symptoms during the first year. At 8 years of age, antibiotic use during the first year of life was significantly associated with wheeze and eczema after adjustment for early life factors. The significant associations at 8 years disappeared following further adjustment for the respiratory infections.

During the first year of life, 43% of the children in our study were exposed to antibiotics, which was moderate compared with previous studies conducted in other western countries [5, 12, 14]. During the same period, 32% of the children had at least one type of respiratory infection among pneumonia, bronchitis and otitis. Antibiotic use and respiratory infections are so common and closely related in early life [17, 18] that it is tricky to consider their individual effect in terms of development of allergic disease.

It has been a long-term discussion whether early antibiotic use is a risk factor for the development of allergic disease. Cross-sectional and retrospective studies often show associations between antibiotic use in early life and asthma condition in childhood [3–11]. Reverse causation cannot entirely be excluded in these studies, as children with early wheeze in infancy are more likely to be prescribed with antibiotics and early wheeze is most likely the true risk factor for asthma. Although children with early asthma symptoms can be excluded from the analysis as it has been applied in previous studies [5, 6], there are

Table 5. Confounding effect of respiratory infection on the relationship between antibiotic use during the first year of life and development of allergic diseases at 8 years of age (adjusted OR and 95% CI)

During first year of life	Wheeze	Asthma	Allergic rhinitis	Eczema	Food hypersensitivity	Any sensitization
Antibiotic use	1.1 (0.9–1.4)	1.2 (0.9–1.5)	1.0 (0.8–1.2)	1.0 (0.9–1.2)	1.0 (0.8–1.1)	1.0 (0.9–1.1)
Pneumonia	0.8 (0.4–1.6)	1.1 (0.5–2.3)	0.9 (0.5–1.7)	1.5 (0.9–2.5)	1.0 (0.5–1.8)	1.1 (0.7–1.8)
Bronchitis	1.6 (1.1–2.4)	1.5 (0.9–2.4)	0.9 (0.6–1.4)	0.9 (0.6–1.3)	1.0 (0.7–1.5)	0.9 (0.7–1.3)
Otitis	1.1 (0.8–1.5)	0.8 (0.5–1.2)	1.2 (0.9–1.6)	1.3 (1.0–1.8)	1.2 (0.9–1.6)	0.9 (0.7–1.2)

Each multivariate logistic regression model consists of antibiotic use during the first year of life, pneumonia, bronchitis and otitis during the first year of life, sex, young maternal age, older sibling, maternal smoking, parental allergy and exclusive breastfeeding.

Table 6. Dose-response effect of antibiotic use during the first year of life on allergic diseases at 4 and 8 years of age in crude and adjusted models (OR and 95% CI)

	One course of antibiotics		Two or more courses of antibiotics		<i>p</i> for trend	
	Crude	Adjusted	Crude	Adjusted	Crude	Adjusted
<i>4 years of age</i>						
Wheeze	1.2 (0.9–1.5)	1.0 (0.8–1.3)	2.2 (1.8–2.8)	1.6 (1.1–2.2)	<0.001	<0.01
Asthma	1.2 (0.9–1.7)	1.1 (0.7–1.6)	2.4 (1.7–3.2)	1.9 (1.2–3.0)	<0.001	<0.01
Allergic rhinitis	1.2 (0.9–1.5)	1.1 (0.8–1.5)	1.3 (1.0–1.7)	1.1 (0.7–1.6)	<0.05	0.63
Eczema	1.2 (0.9–1.4)	1.0 (0.8–1.2)	1.5 (1.2–1.8)	1.1 (0.8–1.5)	<0.001	0.65
Food hypersensitivity	1.3 (1.0–1.7)	1.1 (0.8–1.5)	1.7 (1.3–2.2)	1.3 (0.9–1.9)	<0.001	0.18
Any sensitization	1.0 (0.8–1.3)	0.9 (0.7–1.2)	0.9 (0.7–1.2)	0.8 (0.6–1.1)	0.53	0.19
<i>8 years of age</i>						
Wheeze	1.3 (0.9–1.7)	1.1 (0.8–1.5)	1.8 (1.4–2.4)	1.3 (0.9–1.9)	<0.001	0.16
Asthma	1.1 (0.8–1.6)	1.1 (0.7–1.6)	1.7 (1.2–2.3)	1.5 (0.9–2.4)	<0.01	0.11
Allergic rhinitis	1.1 (0.8–1.3)	0.9 (0.7–1.2)	1.2 (0.9–1.5)	1.0 (0.7–1.4)	0.19	0.81
Eczema	1.3 (1.0–1.6)	1.1 (0.9–1.5)	1.4 (1.1–1.8)	1.1 (0.8–1.5)	<0.01	0.57
Food hypersensitivity	1.4 (1.1–1.7)	1.2 (0.9–1.6)	1.0 (0.8–1.4)	0.8 (0.6–1.2)	0.30	0.60
Any sensitization	1.1 (0.9–1.4)	1.1 (0.9–1.4)	1.0 (0.8–1.2)	0.9 (0.7–1.3)	0.99	0.85

Adjusted OR: adjustment for pneumonia, bronchitis, and otitis during the first year of life, sex, young maternal age, older sibling, maternal smoking, parental allergy and exclusive breastfeeding.

still a number of children with early wheeze unidentified. Even prospective studies need to take the reverse causation into account. For example, in our birth cohort study antibiotic use during the first year was significantly associated with wheeze and asthma at 4 years after adjustment for the early life factors and respiratory infections. The significant associations faded away when the analyses were performed in a subgroup of children without allergic signs during the first year of life, which indicated a reverse causation between antibiotic use and wheeze and/or asthma. Previous prospective studies mostly show no significant association between early antibiotic use and allergy development before or after adjustment for respiratory infection [12–14, 16]. Our findings are in line with the results from these prospective studies and extend further: in addition to the large number of participants and a high follow-up rate of 81% at 8 years of age, our birth cohort study was strengthened by its comprehensive information on allergic diseases including asthma, AR, eczema, food hypersensitivity and sensitization; also, due to the long-term follow-up and longitudinal characteristic of the study design, we could

follow the full development of allergic diseases in childhood [31] and compare the results at two occasions. We were convinced by the consistent findings between 4 and 8 years of age; further, we used a two-step approach of adjustment, which separated the confounding effect of respiratory infection from the early life factors. However, it was difficult to evaluate the individual confounding effect of the three types of respiratory infections as they were overlapping in a number of cases.

Early respiratory infection, particularly lower respiratory tract infection has been associated with an increased risk of allergic disease in previous prospective studies [19–22]. Upper respiratory tract infections, such as the common cold have been suggested to have a reduced risk for allergic disease [20, 21]. Otitis is another common upper respiratory infection usually accompanied with common cold. Despite the difficulty to disentangle the effect of pneumonia, bronchitis and otitis in our study, otitis during the first year of life was consistently associated with an increased risk of eczema both at 4 and 8 years of age. This is in line with a previous study from our birth cohort showing that acute otitis media is

concomitantly associated with atopic dermatitis during the first 2 years of life [32]. Otitis has also been reported to be associated with cow's milk allergy and itself has been argued as an allergic manifestation that progresses to other symptoms of allergic disease [33, 34]. Thus, otitis in early life may be an indication of altered immunity, which leads to eczema later in life. The association between otitis during the first year and later eczema appears robust and cannot be neglected, while the association between bronchitis and wheeze/asthma observed in our study requires a careful interpretation. All in all, we should take caution to draw a general conclusion that early respiratory infections are risk factors for the development of allergic diseases.

The 3306 children included in the present analyses did not differ from the whole cohort in sex or other demographic distribution. Neither did they differ from the 3925 children who participated in the 1-year follow-up in terms of antibiotic use and allergic disease during the first year of life. Therefore, potential bias caused by loss of follow-up is unlikely. A limitation of our study is that we did not have the detailed information on the specific class or spectrum of the prescribed antibiotics. Broad-spectrum antibiotics have been reported to have a stronger impact on asthma than narrow-spectrum antibiotics [5, 35]. We did not have information on the indication for use of antibiotics either. Nevertheless, our results do not suggest a clear association between antibiotic use during the first year of life and development of allergic diseases when findings are taken together: the confounding effect of respiratory infection during the first year on most of the allergic outcomes both at 4 and 8 years of age, the reverse causation on wheeze and asthma at age 4 years and the significant association only with non-IgE-mediated wheeze, asthma and food hypersensitivity at 4 years but not with IgE-mediated allergic symptoms either at 4 or 8 years of age. Lack of information on other respiratory infections, e.g. common cold and flu may be one of the explanations for the partial confounding effect of respiratory infection in the present study.

In summary, our study indicated that the association between antibiotic use during the first year of life and development of allergic disease could at least partially be explained by the respiratory infection during the first year of life. Although they may not be the cause for the development of allergic disease, antibiotics should still be prescribed to children in a sensible way to reduce the increased problem of antibiotic resistance [36]. Certain types of early respiratory infection may lead to symptoms of allergic disease in childhood.

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