

# Antibiotics in the first week of life is a risk factor for allergic rhinitis at school age

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## Keywords

allergic rhinitis; epidemiology; farm living; antibiotics; infant; newborn

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## Abstract

**Background:** Heredity as well as external factors influences the development of allergic rhinitis. The aim of this study was to analyse early risk factors and protective factors for allergic rhinitis at school age.

**Methods:** This is a prospective, longitudinal study of children born in western Sweden in 2003 where 50% of the birth cohort was randomly selected. The parents answered questionnaires at 6 months, 12 months, 4.5 yr and 8 yr. At 8 yr, 5044 questionnaires were distributed. Of these, 4051 responded, that is, 80.3%. Current allergic rhinitis was defined as symptoms and use of medication during the past 12 months.

**Results:** Current allergic rhinitis at 8 yr was reported by 10.9%. Mean onset age was 5.7 yr, and 61.9% were boys. In a multivariate analysis, antibiotics in the first week of life increased the risk of allergic rhinitis (adjusted odds ratio 1.75, 95% confidence interval (1.03, 2.97)). Increased risk was also seen with parental allergic rhinitis (aOR 2.73 (2.12, 3.52)), food allergy first year (aOR 2.45 (1.61, 3.73)), eczema first year (aOR 1.97 (1.50, 2.59)) and male gender (aOR 1.35 (1.05, 1.74)). Living on a farm at 4.5 yr reduced the risk (aOR 0.31 (0.13, 0.78)).

**Conclusion:** Antibiotics in the first week of life increased the risk of allergic rhinitis at school age, while living on a farm at preschool age reduced the risk. Both findings are compatible with the hygiene hypothesis.

The hygiene hypothesis, originally suggested by Strachan (1), implies that microbial pressure in early life protects against atopic disease by suppressing T-helper 2 immune responses, thus shifting the response towards Th1 domination. This highlights the importance of the gut microbiota (2). Changes in the gut microbiotic flora, by means of, for example, antibiotic treatment in early life, have been associated with an increased prevalence of allergic diseases (3). Growing up on a farm (4, 5) has also been associated with a reduced prevalence of allergic diseases. In a recent paper reporting a western Sweden setting (4), it was shown that growing up on a farm confers lifelong protection against allergic rhinitis.

In a previous paper from this cohort, we studied early factors that affect the risk of allergic rhinitis at 4.5 yr (6). In that study, we found that rural living and antibiotics in the first week of age had a significant effect in the univariate analysis, but not after adjusting for a large number of potential confounders. In this paper, the aim was to study early risk factors and protective factors for allergic rhinitis at school age in the same cohort.

## Methods

Data were obtained from a prospective, longitudinal cohort study of children born in the region of western Sweden in 2003. The region has 1.5 million inhabitants, one-sixth of the Swedish population. It comprises urban as well as rural areas. The largest city is Gothenburg, with 500,000 inhabitants.

The yearly birth cohort in Western Sweden in 2003 was 16,682 infants. For economical and practical reasons, 50% of the cohort was randomly selected and sent an invitation to participate in the study. The parents answered questionnaires at 6 months and 1, 4.5 and 8 yr of age. Supplementary data were taken from the Swedish Medical Birth Register (MBR). The questionnaires were based on the Swedish version of ISAAC and the Swedish BAMSE study. Details regarding the questionnaires and earlier response rates have been published previously (6–10).

At 8 yr, questionnaires were distributed to the families entering the study ( $n = 5654$ ), except for those that had declared that they no longer wished to participate ( $n = 610$ ),

that is, 5044. Of these, 4051 returned the questionnaire, that is, 80.3% and 4033 responded to the question regarding allergic rhinitis (question 1, below).

Information on pregnancy and post-natal factors was collected at 6 months of age. Supplementary information about pregnancy and delivery was obtained from the MBR and gave information on caesarean section, gestational age, small for gestational age, large for gestational age, gender and Apgar score.

Information on admission to a neonatal ward during the first week of life and treatment with broad-spectrum antibiotics during this period was obtained from the 6-month questionnaire. Information on the duration of breastfeeding and introduction of different foods was collected at 12 months. Specific information about these questions has been published previously (7). The question in the 4.5-yr questionnaire concerning farm living was as follows: 'Do you live on a farm with animals?' At 8 yr, questions were asked regarding current health and disease, family, environment and feeding habits.

The questions related to allergic rhinitis in the questionnaire were as follows:

- 1 'Has your child experienced hay fever or allergic rhinitis (sneezing, runny nose, nasal blockage or red and itching eyes) during the last 12 months?'
- 2 'Has your child used any medicines for hay fever during the last 12 months (pills, nasal spray or eye drops) for these symptoms?'
- 3 'Has your child been diagnosed with hay fever or allergic rhinitis by a doctor?'
- 4 'How old was your child when the symptoms [of rhinitis] began? YY?MM?'

'Allergic rhinitis' was defined as the group of infants whose parents answered yes to questions [1] and [2]. The reason not to use a doctor's diagnosis in the definition is that many children use over-the-counter drugs without a doctor's diagnosis to alleviate symptoms of allergic rhinitis. In our material, only 46.2% of the children with medication for rhinitis had doctor-diagnosed allergic rhinitis.

### Statistical methods

In the univariate statistical analysis,  $2 \times 2$  tables with the  $\chi^2$ -test were used and risks were estimated using the Mantel-Haenszel common odds ratio estimate. In the multivariate analysis, forward stepwise binary logistic regression was used and odds ratios (OR) with 95% confidence intervals (CI) were calculated. Variables with an association with allergic rhinitis ( $p < 0.1$ , Table 1) were included in the subsequent multivariate model.

Patterns of trigger factors for allergic rhinitis were analysed by K-means cluster analysis in SPSS (11). The reason to choose five clusters was to avoid too few individuals in the least frequent clusters.

The SPSS v. 21 statistical package was used for the statistical calculations.

### Ethical approval

The study was approved by the Ethics Committee, University of Gothenburg. All parents provided written informed consent.

**Table 1** Independent risk factors for allergic rhinitis at school age

Variable	OR	95% CI
Living on a farm with animals at preschool age	0.31	0.13, 0.78
Parental allergic rhinitis	2.73	2.12, 3.52
Doctor-diagnosed food allergy first year	2.45	1.61, 3.73
Eczema first year	1.97	1.50, 2.59
Antibiotics in the first week of life	1.75	1.03, 2.97
Male gender	1.35	1.05, 1.74

Variables in the model were as follows: maternal age  $<25$  yr, paternal education  $>12$  yr, rural residence first year, living on a farm at preschool age, daily outdoor time, parental asthma, parental rhinitis, parental eczema, maternal medication during pregnancy, neonatal antibiotics, large for gestational age, cat in the home first year, dog in the home first year, fish consumption  $>1 \times$ /month first year, fermented food  $>1$ /month, eczema first year, doctor-diagnosed food allergy first year, recurrent wheeze at 12 months of age, pacifier first year and gender.

## Results

### Prevalences

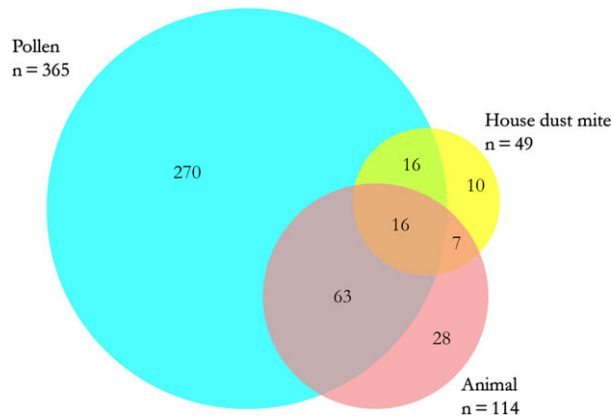
At 8 yr of age, 14.0% (564/4033) of the children reported symptoms of rhinitis during the last year, where boys were 61.1% and girls 38.9%. Use of medications and symptoms was reported in 10.9% ( $n = 441$ ), and 5.7% ( $n = 228$ ) had a doctor's diagnosis. Of the children reporting use of medications, the mean onset age was 5.7 yr (range 0–8.5 yr).

Of the 441 infants reporting medication and rhinitis ('current allergic rhinitis'), 410 had responded to the question: 'What triggered the symptoms?' Reported trigger factors were (in descending order) tree pollen ( $n = 264$ , 64.2%), grass pollen ( $n = 259$ , 63.2%), cat ( $n = 84$ , 20.5%), house dust mite ( $n = 49$ , 14.4%), dog ( $n = 55$ , 13.4%), horse ( $n = 36$ , 8.8%) and rodents ( $n = 20$ , 4.9%). It was possible to check more than one trigger in the questionnaire. The combinations of trigger factors are shown in Fig. 1.

In the cluster analysis, the five combinations of trigger factors were as follows: tree and grass pollen (32.4%), tree pollen (23.6%), grass pollen (24.1%), cat and house dust mite (7.5%), cat, dog, tree and grass pollen (6.6%), cat, dog and horse (5.8%).

### Univariate and multivariate analyses

A large number of potential risk factors for rhinitis and allergic disease were tested in univariate models. We found no associations ( $p > 0.1$ ) with parity 3+, cohabitation at birth or at 6 months, maternal education, housing, mould or dampness in the house, air pollution, attended maternity care, access to summer house, maternal alcohol use during or after pregnancy, low birth weight, admission to neonatal ward, temperament first week and at 6 months, smoking during pregnancy, bird or rodent keeping first year, breast feeding less than 4 months, introduction of fish before 9 months, introduction of egg before 9 months, type of spread, type of fat used in cooking,



**Figure 1** Venn diagram of the prevalence of the trigger factors animals, house dust mites and pollens of allergic rhinitis at 8 yr of age in western Sweden. The diagram shows the observed combinations of the triggering allergens.

type of fish consumed (lean/fat), vegetarian diet in family, AD-vitamin supplementation, adherence to vaccination programme, caesarean section or preterm birth.

Associations ( $p < 0.1$ ) with allergic rhinitis was found with maternal age, paternal education, rural residence first year, living on a farm with animals at preschool age, daily outdoor time, family history of allergic disease, exposure to cat and dog first year, frequent consumption of fish and fermented food, allergic disease first year, maternal medication during pregnancy, neonatal antibiotics, large for gestational age, pacifier and gender (Table S1).

In the multivariate analysis of the factors with an association with  $p < 0.1$  in the univariate analyses, we found that antibiotics in the first week of life increased the risk (aOR 1.75 95% CI (1.03, 2.97)), while living on a farm with animals at 4.5 yr reduced the risk (0.31 (0.13, 0.78)). The risk also increased with family history, early disease and male gender (Table 1).

In the comparison between responders and non-responders of the questionnaire distributed at 8 yr, we found that the non-responders were less likely to have a family history of allergic disease, to have a parent with an education of more than 12 yr and to breastfeed longer than 4 months. They were more likely to have been exposed to nicotine *in utero* and to be preterm (Table 2).

## Discussion

The main findings of this study were that antibiotic treatment during the first week of life increased the risk of current allergic rhinitis at 8 yr of age and that a farming environment at preschool age emerged as a protective factor. Both findings are compatible with the hygiene hypothesis. Other independent risk factors were a family history of allergic rhinitis, early food allergy, early eczema and male gender.

Our definition of allergic rhinitis is very similar to the definitions used in the ISAAC study (12) and that of Kull et al. (13) in the BAMSE study in that none uses a doctor's diagnosis, which has been used in other studies (14, 15). In our previous study of rhinitis at 4.5 yr of age (6), we chose not to include a doctor's diagnosis in the definition because very few infants had been diagnosed with allergic rhinitis at that age and this would give a very low power. At the 8-yr follow-up, we had information on whether the child had taken medicines for its symptoms and therefore included this in the definition. Contributing to this decision was our finding in the material that many children of school age are treated with over-the-counter preparations of anti-allergic drugs.

In this study, the prevalence of allergic rhinitis with medication was almost 11%, which corresponds well to other studies. In a recent study from Stockholm (16), medication for allergic rhinitis in children aged 8 yr was reported by about 13% of parents. In 2004, the prevalence in 6- to 7-yr-old children according to ISAAC was 6.9% in Sweden compared with 8.5% (range 1.8–20.4%) in the total material of 6- to

**Table 2** Responders vs. non-responders of the questionnaire distributed at 8 yr

	Responders (n = 4051)		Non-responders (n = 1603)		p
	n	%	n	%	
Family history of asthma, rhinitis or eczema	2452	60.9	869	55.2	<b>&lt;0.001</b>
Parental education > 12 yr	2494	62.1	695	44.4	<b>&lt;0.001</b>
Male gender	2127	52.6	733	50.8	0.25
Maternal smoking during pregnancy	308	7.7	228	14.6	<b>&lt;0.001</b>
Maternal medication during pregnancy	1131	28.2	449	28.8	0.66
Gestational age < 37 weeks	204	5.1	90	6.9	<b>0.016</b>
Caesarean section	571	14.3	184	14.2	0.94
Treatment with antibiotics the first week in life	187	4.7	66	4.2	0.45
Breastfeeding 4 months or more	2696	80.4	749	73.1	<b>&lt;0.001</b>
Wheeze during the first year	735	19.6	260	22.1	0.06
Doctor-diagnosed food allergy during the first year	178	4.7	63	5.3	0.40
Eczema during the first year	784	20.8	249	21.0	0.89

Significant differences in bold style.

7-yr-old children. Among 13- to 14-yr-old children, the prevalence in Sweden was 10.4% compared with 14.6% (1.4–33.3%) (17).

We found that pollen was the most commonly reported trigger, followed by animals. The cluster analysis revealed that the three most common variants of trigger factors were combinations of tree and grass pollen. Few cases of allergic rhinitis at this age were triggered by house dust mite. This is partly in line with the OLIN study (18), in which a low prevalence of sensitization for mite was found. However, they found a higher prevalence of sensitization to animals than to pollen. A low prevalence of mite sensitization was also found in the BAMSE study from Stockholm (19). The Tucson study (20) reported that sensitization to pollen was more common than sensitization to animals.

The 'hygiene hypothesis', as originally suggested by Strachan, was that early childhood infections were acquired by 'unhygienic contact with older siblings, or acquired prenatally from a mother infected by contact with her older children' (1). Other environmental influences than the number of siblings have since been proposed, among these the different lifestyles in western and eastern Europe.

It has been shown that atopic disease is much more rare in Estonia and Russian Karelia than in Western Europe and Finnish Karelia (21), suggesting an environmental influence, possibly urbanization and less contact with environmental micro-organisms in Western Europe and Finnish Karelia.

This suggests that early antibiotic interventions could also have an effect on the development of asthma and allergic disease, which has in fact been shown in several studies in different countries (3), although not all (22).

Related to the 'hygiene hypothesis' is the 'microflora hypothesis', where a low diversity of the infant gut microbiota has been linked to an increased risk of allergic disease (23). Björkstén et al. (24) showed that allergic children more often had coliform bacteria and *S. aureus*, whereas non-allergic children significantly more often harboured lactobacilli.

However, there has been criticism of studies that show an association between antibiotic treatment and allergic disease, as the findings may be subjected to reverse causation (antibiotics are given as a treatment in the first episodes of asthma) or confounding by indication (antibiotics are given as a treatment of a disease that is associated with asthma) (25). In our cohort, we have seen that antibiotic treatment during the first week increased the risk of wheeze or asthma at 1, 4 and 8 yr of age (7, 9, 10). To avoid the risk of reverse causation, we chose broad-spectrum antibiotics given in the first week of life as the exposure variable in our studies. An increased risk of allergic rhinitis has also been shown (26), although reverse confounding cannot be ruled out in those studies as the exposure variable was antibiotic treatment during the first year of life.

When investigating the effect of farm living on future incidence of allergic disease, it is important to bear in mind the possibility of a reverse causation, or a so-called 'healthy worker's effect' (27). This means that there is a selection of people without allergy in the population of farmers, which

could lead to a lower prevalence of allergic disease among infants from a farming environment.

One interesting observation was that we found no effect of admission to a neonatal ward in the univariate analysis (Table 1). It is common for admission to a neonatal ward and early antibiotics to covariate, especially when analysing effects on asthma, as the admission very often leads to treatment with antibiotics. The finding suggests that the effect seen is more likely to be caused by early antibiotics *per se*, and not by the fact that the infant's health is compromised in some other way.

Bacterial endotoxins are wall components from gram-negative bacteria, and very common in the environment, especially where animals and agricultural products are handled. Exposure to endotoxins has long been known to correlate inversely with the severity of asthma (28). It has also been shown that exposure to endotoxins, by inducing interferon gamma and interleukin 12 production, promotes Th1-type and inhibits Th2-type immune responses (29), thereby possibly suppressing the development of allergy and asthma. It has been found that endotoxin levels are higher in Estonia than in Sweden, thus supporting the hypothesis (21).

There are several studies that find a protective effect on asthma and allergies of a farm environment (5, 30), which could be attributed to endotoxin exposure. The West Sweden Asthma Study found a lifelong protective effect on allergic rhinitis as a result of growing up on a farm during the first 5 yr of life (4).

The responding families of the 8-yr questionnaire were, as also was the case in the 4.5-yr follow-up (9), smoking less, breastfeeding more and had a higher education, which might suggest a more health-conscious lifestyle. This might lead to some bias in the sample; however, these differences have not changed since the 4.5-yr follow-up (9).

### Weaknesses and strengths

A weakness of the study is that the data were collected by postal questionnaires. As a result, the end-point is not objectively measured. Questionnaire-based studies are also accompanied by limitations relating to the validity and interpretation of the answers. To avoid this, we used questions based on well-known, validated questionnaires. As is often seen in questionnaire studies, responders were somewhat more health conscious and educated compared with non-responders (10).

The strengths are the large size of the birth cohort, access to perinatal data and the good response rate of 80% to the questionnaires distributed and more than 70% of those initially entering the study. In all, we have data from all the questionnaires relating to over four thousand children. Moreover, as reported earlier, the material appears to be representative of the population (7).

### Conclusions

In conclusion, we found that antibiotics in the first week of life increased the risk of allergic rhinitis at school age and observed

a protective effect of living on a farm at preschool age. Both findings are compatible with the hygiene hypothesis. In addition to antibiotics in the first week of life, we found that a family history of allergic rhinitis, early food allergy, early eczema and male gender increased the risk of allergic rhinitis at school age.

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## Supporting Information

Additional Supporting Information may be found in the online version of this article:

**Table S1.** Variables with an association with allergic rhinitis ( $p < 0.1$ ) in the univariate analysis with prevalences and ORs.