Published in final edited form as:

J Allergy Clin Immunol. 2009 August ; 124(2): 357–6415. doi:10.1016/j.jaci.2009.05.011.

Major increase in allergic sensitization in school children from 1996 to 2006 in Northern Sweden

Eva Rönmark, PhD^{1,2}, Anders Bjerg, MD, PhD^{1,3}, Matthew Perzanowski, PhD⁵, Thomas Platts-Mills, MD, PhD⁶, and Bo Lundbäck, MD, PhD^{1,4}

¹The OLIN Studies, Department of Medicine, Sunderby Central Hospital of Norrbotten, SE-971 89 Luleå, Sweden

²Department of Clinical Medicine and Public Health, Occupation & Environment, University of Umeå, 90185 Umeå, Sweden

³Department of Clinical Medicine and Public Health, Respiratory Medicine & Allergology, University of Umeå, 90185 Umeå, Sweden

⁴Department of Internal Medicine, Respiratory Medicine & Allergology, Sahlgrenska Academy, University of Gothenburg, SE - 413 45 Gothenburg, Sweden

⁵Department of Environmental Health Sciences, Columbia University, New York, USA

⁶Asthma and Allergic Diseases Center, University of Virginia, Charlottesville, USA.

Abstract

Background—Time trends for allergic sensitization are poorly known.

Aim—To compare the trends in prevalence of allergic sensitization and associated risk factors in children.

Methods—Two cohorts of children (age 7–8 years) were invited to skin prick testing (SPT) ten years apart, 1996 and 2006. Participation rate was 2148 (88%) and 1700 (90%), respectively. The methods were identical and ten common airborne allergens were used. An expanded ISAAC-questionnaire about symptoms and possible risk factors for allergic conditions was completed by the parents.

Results—The prevalence of any positive SPT increased from 21% in 1996 to 30% in 2006 ($p < 0.001$). The pattern of sensitization remained similar, and sensitization to cat was most common both years, 13% and 19%, respectively. Sensitization to mites and mould were uncommon in both surveys. A family history of allergy was a significant risk factor for a positive SPT both years (OR 1.7). Factors that in 1996 had a protective effect, i.e. rural living and having several siblings, had lost

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Corresponding author: Eva Rönmark, PhD, associate professor, Dept of Clinical Medicine and Public Health, Occupation & Environment, University of Umeå, SE-90 185 Umeå, Sweden, Phone: +46-70-5424431, +46-920-284483, Fax: +46-920-230843, E-mail: eva.ronmark@telia.com.

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Conflict of interest: No author has any conflict of interest to declare.

Capsule summary:

A 45% increase in allergic sensitization was found among school children by two surveys ten years apart. No parallel increase in allergy symptoms was seen: possibly due to decreases in environmental tobacco smoke, and respiratory infections.

this effect in 2006. The prevalence of most risk factors remained similar, but respiratory infections and smoking among parents decreased significantly. During the same period there was no significant increase in prevalence of current wheeze (11.9% to 12.4%, n.s.) or symptoms of rhinitis or eczema.

Conclusion—The prevalence of allergic sensitization increased significantly from 1996 to 2006, while no increase in clinical symptoms was found. The parallel decrease in parental smoking and respiratory infections indicate a different influence of environmental factors on allergic sensitization and clinical symptoms, respectively.

Keywords

allergic sensitization; atopic disease; epidemiology; OLIN; school children; skin prick test

INTRODUCTION

After decades of an increase in the prevalence of allergic diseases ¹, recent studies report no further increase in asthma in countries with a high prevalence ². Although asthma is strongly related to allergic sensitization ³, most studies of diseases related to allergy have been focused on asthma. Furthermore, most studies are questionnaire based, and a part of the increase of asthma may be attributable to increased awareness in the population and changed diagnostic criteria rather than a true increase ⁴. Objective measures of allergic sensitization are therefore of great importance. Skin prick test (SPT) reactivity is a valid and useful method in epidemiological studies, but has only rarely been applied to large samples from the general population with identical methods at different time points, which is necessary when studying time trends.

The few recent studies evaluating time trends of allergic sensitization in children show diverging results. Studies performed in Australia and European countries ^{5–9} report a stable prevalence or a decrease, while an increase has been reported from Greenland ¹⁰ and Ghana ¹¹. The current situation regarding allergic sensitization in Sweden and other Northern European countries is unknown.

Although some risk factors for allergic sensitization are known, the reasons for changes in the prevalence of allergic sensitization are not known. While a heredity component is the most important known risk factor ^{12,13}, several “protective” factors have been found. Rural living ^{12,14}, close contact with livestock ¹⁵, having several siblings ¹⁶, and according to some studies but not others, keeping a cat or dog at home ^{12,17–19} are reported to be negatively associated to allergic sensitization. Recent studies suggest that un-pasteurized milk ²⁰ and a high content of micro-organisms in drinking water ²¹ may be associated with a decreased risk of allergic sensitization. Furthermore, children with an anthroposophic lifestyle have been reported to have less allergic diseases ²².

In 1996 a large cohort of 7–8 year old children in Northern Sweden was extensively examined. The prevalence of allergic sensitization was 21% measured by skin prick test, 6% were diagnosed as having asthma, and 12% reported current wheeze ²³. A new cohort of the same age living in the same areas was examined in 2006 using identical methods. The aim of the study was to investigate time trends in the prevalence and risk factor patterns of allergic sensitization among 7–8 year old children from 1996 to 2006.

METHODS

Study population

The study includes two cohort studies within the research program Obstructive Lung Disease in Northern Sweden (OLIN). In 1996²³ and 2006 all children in the first- and second-grade classes aged 7 and 8 years in two municipalities in Northern Sweden were invited to participate in skin prick testing (SPT) and a questionnaire study. Due to lower birth rates, the cohort from 2006 was somewhat smaller. The participation rate in the SPT in 1996 was 2,148 (88%), and 1700 (90%) children participated in 2006 with similar participation rate among girls and boys, and in the two areas. Consent for the SPT was obtained from the children's parents. The Ethical committee of Umeå University approved the studies.

Questionnaire

A parental questionnaire based on the ISAAC design²⁴, which has been described previously²³, was used. Additional questions were included aiming at screening for possible risk factors including family history of allergic diseases, number of siblings and birth order, birth weight, length of breast feeding, respiratory infections, past or present pets at home, parental smoking, house dampness, and other living condition factors (see this article's Online Repository at www.jacionline.org). The questionnaire was distributed by the school teachers. The variable *any respiratory infection* included a report of croup, respiratory syncytial (RS) virus, pertussis infection, or pneumonia. The variable regarding length of breast-feeding included both exclusive and non-exclusive breast feeding. Asthma was defined as a positive answer to the question; "Has your child been diagnosed by a physician as having asthma?"

Skin prick tests

The SPT were carried out from February to April both in 1996 and 2006 in the schools by a small specifically trained staff following the European Academy of Allergology and Clinical Immunology recommendations²⁵. The following allergens were used; birch, timothy, mugwort, dog, cat, horse, *Dermatophagoides farinae*, *D. pteronyssinus*, Cladosporium and Alternaria (Soluprick, ALK, Hørsholm, Denmark). The potency of the extracts was 10 HEP, except the two moulds, which were 1:20 w/v. The manufacturer certified that the potency and the allergen content had not changed between 1996 and 2006. Histamine 10mg/ml and glycerol were used as positive and negative controls. A positive reaction was recorded if the wheal was ≥ 3 mm after 15 minutes. A positive reaction to any of the tested allergens was defined as *any positive SPT*. In addition the prevalence of positive SPT was calculated by using a cut off of ≥ 4 mm.

Serum samples

The SPT results from 1996 have been validated against specific IgE²⁶, and a validation study of the skin prick results from the 2006 study was performed in November 2006 in a sub-sample. All children with *any positive SPT* in four schools in Luleå were invited to a second SPT, and sera were taken for analyses of specific IgE antibodies. Of 59 participating children in the second SPT, sera were available from 50 children. Specific IgE antibodies to birch, timothy, cat, dog and horse were measured by the CAP system, Phadia, Uppsala, Sweden, and allergen specific IgE concentrations ≥ 0.35 IU/ml were considered positive.

Analysis

Statistical analyses were performed using the Statistical Package for Social Sciences (SPSS) for Windows, release 14.0. Chi-squared test was used for bi-variate comparisons of categorical variables and one-way ANOVA for test for trend. A p-value < 0.05 was considered statistically significant. Multiple logistic regression analyses were used to estimate the prevalence change

of positive SPT from 1996 to 2006 after adjustment for potential confounders. Risk factors for a positive SPT were calculated using multiple logistic regression analyses and expressed in Odds ratios (OR) with 95% confidence intervals (95%CI). Independent variables significantly associated with allergic sensitization in the bi-variate analyses were included in the multivariate model. The effects of having *any sibling*, *any infection*, and *rural living*, respectively, was also evaluated in different categories defined as follows; no asthma and negative SPT (reference), asthma but negative SPT (non-allergic asthma), no asthma but positive SPT, and asthma and positive SPT (allergic asthma).

RESULTS

Prevalence

The prevalence of *any positive SPT* increased from 20.6% in 1996 to 29.9% in 2006, $p<0.001$. The pattern of allergic sensitization was similar in 1996 and 2006, and sensitization to cat was most common both years, 13.4% and 19.1%, respectively. A positive SPT to mites and moulds was uncommon both in 1996 and 2006 (Table 1). The increase from 1996 to 2006 expressed as odds ratios after correction for confounders is displayed in Figure 1. Among the most common allergens, the increase was largest for a positive test to dog, OR 1.94 (1.57–2.39). In 2006 *any positive SPT* was significantly more common among boys, 32.6% versus 27.2% in girls ($p<0.001$), and a positive SPT was more common among boys for nearly all tested allergens (Table 1). When a cut off level of 4mm was used to define a positive SPT, the prevalence of any positive SPT was 15.1% in 1996 and 22.9% in 2006 ($p<0.001$).

The prevalence of children sensitized to each of any, two, three, or more allergens increased from 1996 to 2006. Further, the proportion of multi sensitized children increased (Figures 2). The mean size of the reactions were similar in 1996 and 2006; birch 4.7mm and 4.6mm, timothy 4.7mm and 4.8mm, dog 4.4mm and 4.5 mm, and cat 5.6mm both years. The reaction to histamine was slightly larger in 2006 compared to 1996, 4.7mm versus 4.1mm ($p<0.001$).

Determinants of allergic sensitization

From 1996 to 2006 there were changes in the prevalence of possible risk factors. Significantly fewer children had ≥ 2 siblings in 2006 compared to 1996, 42.4 versus 51.0%. An inverse association between increasing number of siblings and *any positive SPT* was found in 1996 but not in 2006. A family history of allergy increased slightly from 45.4 to 48.7%, and was significantly associated with *any positive SPT* in both 1996 and 2006 (Table 2).

Having a cat or dog in the home was inversely associated with *any positive SPT* both years. Among children with a family history of allergy, the proportion of ever having had a cat in the home decreased from 23.7% in 1996 to 19.5% in 2006 ($p=0.008$), while for dog this proportion was the same both years; 29.5 and 29.9%. In 1996, living on a farm, rural living, or rural living the first year of life were all negatively associated with a positive SPT, however, non of these associations reach statistical significance in 2006 (Table 2).

The proportion of smoking parents decreased significantly, from 31.8 to 15.5% (mothers) and 21.6 to 12.9% (fathers). Similarly, the prevalence of any respiratory infection decreased from 58.4 to 28.1%, and of pertussis infection from 44.6 to 2.4%. When pertussis infection was excluded from the variable any respiratory infection, the prevalence was 28.8% in 1996 and 26.6% in 2006 ($p=0.063$). The proportions reporting dampness at home and breast-feeding <3 months also decreased significantly (Table 2). No significant association between number of siblings and respiratory infections were found (see Table E1 in this article's Online Repository at www.jacionline.org).

Multivariate relationships

A family history of allergy was the most important risk factor for *any positive SPT* both in 1996 and 2006 (Table 3a). Ever having had a cat at home was inversely related to any *positive SPT* both in 1996 and 2006, OR 0.66 and 0.71, respectively. Living on a farm and having three or more siblings were both significantly associated (negatively) with any positive SPT in 1996, OR 0.29 (0.09–0.94) and OR 0.50 (0.31–0.82), while neither association was significant in 2006. Living close to a heavy traffic road was a risk factor for sensitization in 2006, OR 1.28 (1.02–1.59), but not in 1996. The risk for sensitization to any animal and any pollen showed a similar pattern (Table 3b).

Effect of risk factors on clinical conditions

Having at least one sibling was a protective factor against allergic asthma both in 1996 and 2006, while no effect was seen on non-allergic asthma or on sensitization without asthma (Table 4). A report of any respiratory infection was a strong risk factor for non-allergic asthma in particular, but also allergic asthma, both in 1996 and 2006, while no effect was found among those with a positive SPT without having asthma. Rural living was protective against a positive SPT irrespectively of having asthma or not in 1996 while no specific pattern was found in 2006.

Associations between positive SPT and asthma, rhinitis, and eczema

The prevalence of wheezing during the last 12 months, symptoms of rhinitis, and symptoms of eczema did not increase significantly between 1996 and 2006; 11.9 to 12.4% ($p=0.636$), 14.5 to 15.1% ($p=0.550$), and 29.3 to 26.5% ($p=0.048$), respectively. Having *any positive SPT* significantly increased the risk for symptoms of asthma, rhinitis, and eczema both in 1996 and 2006 with no major changes in the magnitudes between the study years (data not shown).

Validation study

The agreement between the first and the second SPT in 2006 was excellent. Of the children with *any positive SPT* in the first test, 95% also presented this result in the second test. As in 1996²⁶, the correlation was excellent also between SPT and specific IgE in 2006. In 88% of the children with a positive SPT (wheal size of ≥ 3 mm) to any of the tested allergens, IgE ≥ 0.35 IU/ml to any of the corresponding allergens could be detected. Details of the results from the validation study are presented in Table E2 in this article's Online Repository at www.jacionline.org.

DISCUSSION

This study found a significant increase from 21% to 30% in the prevalence of allergic sensitization in 7–8 years old children in Northern Sweden from 1996 to 2006. The pattern of sensitization remained similar and sensitization to cat was most common in both years. Despite the large increase in the prevalence of allergic sensitization, no increase in the prevalence of symptoms of asthma, rhinitis or eczema was found, which could be a result of a reduction in other well known risk factors for asthma, including parental smoking, home dampness and respiratory infections. These results emphasize the difference between allergic sensitization and clinically relevant allergy. To our knowledge, this is the first study comparing trends in risk factors to changes in allergic sensitization.

The few recent studies evaluating time trends of allergic sensitization in children show diverging results^{5–11} (Figure 3). While most studies from westernized countries showed a plateau or a decrease in prevalence our study showed a significant increase in sensitization to all common allergens in the area. A study from the former East-Germany reported conflicting

results as the prevalence of any allergic sensitization decreased, while “strong sensitization”, defined as $\text{RAST} \geq 17.5 \text{ kU} \cdot \text{L}^{-1}$ increased²⁷. The relative absence of mite in Northern Sweden is confirmed by analyses of allergens in dust from homes and schools²⁸.

Our result is indirectly in line with the hygiene hypotheses^{16,29}. According to this hypothesis, allergic sensitization should be related to lack of infections and microbial products in early age due to a shift in the balance of T-helper cells towards type-2 (Th2) cells³⁰. Parallel to the increase in allergic sensitization we found decrease in family size, fewer smoking parents, increase in breast feeding and a better indoor climate. These factors are all related to less frequent infections in childhood, and we also found a significant reduction in respiratory infections. On the other hand, taken one by one, none of these factors, with the exception of number of siblings, was related to allergic sensitization.

The dramatic decrease in respiratory infections was mainly attributable to a decrease in pertussis infections, a result of the re-introduction of general vaccination against pertussis among new-born children in 1996. Thus, the first cohort (born 1987–88) was not immunized, while the second cohort (born 1997–98) was. The decrease in reported pertussis infections corresponds well with data from The Swedish Institute for Infectious Disease Control³¹. Theoretically, vaccination in general could result in increased risk for allergic sensitization and thus explain the higher prevalence of allergic sensitization in the 2006 cohort. However, a double blind study performed in Sweden³², and a large population study in England³³ did not show any association between immunization to pertussis and allergic sensitization or allergic disease.

In 1996, allergic sensitization was inversely associated with increased number of siblings, as reported by others^{16,29}, but ten years later this association was less prominent. It has been shown that children with several siblings are more affected by infections²⁹. However, in our study respiratory infections were not related to the number of siblings in either cohort. As shown in table 4, the effect of number of siblings and respiratory infections diverged. Respiratory infections had a large impact on the development of asthma but not on sensitization itself, while the sibling effect acts in the opposite way. Thus, our study does not support the theory that a decrease in infections is responsible for the increase in allergic sensitization. However, a weakness in our study is the limited information about the type of infections, which could be of importance. The explanation for the relationship between number of siblings and allergic sensitization remains unclear and may be related to other unknown factors.

In this study, living in rural areas was a protective factor against allergic sensitization in 1996²³. This has been demonstrated previously¹¹, but in our first cohort this protective effect disappeared with increasing age¹², similar to a previous Swedish finding³⁴. The loss of a protective effect of rural living may be related to changes in rural lifestyle towards urban regarding factors such as diet, stress etc. The effect of outdoor pollutants on allergic sensitization is not clear, but a recent study reported a significant association between ambient particulate matter and allergic sensitization³⁵. This relationship may also reflect the lower prevalence of allergic sensitization found in rural compared to urban areas¹⁴.

The progress from allergen exposure to development of allergic sensitization is not clear, and several studies have reported a negative association between pet keeping and the development of asthma and allergic sensitization^{17–19}. The negative association is partly a result of selection bias, as families with asthma or allergy more often avoid having pets^{19,36}. Data from the ECRHS have showed that the numbers of cats in the population positively correlates to the prevalence of asthma or allergy in the population, while at an individual level, cat owners had less prevalence of asthma compared to non-cat owners³⁷. In our study, the prevalence of keeping cat or dog was similar in 1996 and 2006. In high-risk children however, cat keeping

was less common in 2006. Thus the increase in prevalence of allergic sensitization was not due to increased allergen exposure. Indeed, the current results further strengthen the complexity of the relationship between allergen exposure and allergic sensitization.

A family history of allergy increased slightly, however not correspondingly to the increase in allergic sensitization, suggesting that the increase probably is related to environment or lifestyle rather than changed genetic predisposition. Also the 10 year perspective argues against a change in genetic predisposition. While smoking among the parents decreased significantly due to several governmental measures, smoking was not related to a positive SPT, and most studies have not identified parents' smoking to be associated with allergic sensitization³⁸.

As a consequence of the strong relationship between wheeze and allergic sensitization^{3,39}, one would expect parallel time trends. The stable prevalence of wheeze despite the increase in allergic sensitization may be a result of the marked decreases in other well known risk factors for asthma in children including maternal smoking, home dampness, and as previously noted respiratory infections. These factors are all related to childhood asthma and wheeze^{23,29,39,40}.

Although we were not able to use allergen extracts from the same batches in the two studies performed ten years apart, the validity of the results are supported by the large sample size, the high participation rate, and the good correlation between SPT results and specific IgE both in 1996²⁶ and 2006. The similar mean wheal sizes of the positive reactions in 2006 compared to 1996 further support the validity of the results. The small increase of the histamine wheal size may however reflect some methodological bias. An increase in skin reactivity to histamine over time has also been reported by Ronchetti *et al*⁴¹, and they suggest this could be a result of increased skin cellular or neurogenic inflammation. Nevertheless, this hypothesis remains to be proved and is still not supported by others⁴².

In conclusion, this study of two large cross-sectional studies of schoolchildren of the same age in the same area of Sweden performed ten years apart with identical methods and high participation rate found a significant increase in prevalence of allergic sensitization measured by skin prick test. In parallel, the prevalence of allergy symptoms did not change: possibly a result of improvements in the environment, mainly environmental tobacco smoke, and respiratory infections. Although no increase in symptoms of allergy, the large increase in sensitization may predict a continuous increase in clinical manifestations of allergic diseases in pre-teenage and teenage years. The new cohort will be closely followed.

Key Messages

- The prevalence of allergic sensitization increased 45% in school children over a ten year period
- Parallel, the prevalence of allergy symptoms did not change: possibly due to improved environment.
- The large increase in sensitization may however predict an increase in clinical manifestations of allergic diseases in pre-teenage and teenage. The new cohort will be carefully followed.

ACKNOWLEDGEMENTS

The authors express gratitude to the cohort participants and their parents, and to the research team within the OLIN studies, especially Kerstin Kemi-Björnström, Lena Gustafsson, Aina Johnsson, Sigrid Sundberg and Linnea Hedman.

Founding: The study was founded by The Swedish Heart-Lung Foundation, the Swedish Foundation for Health Care Science and Allergy Research (Vårdal), the Swedish Asthma-Allergy Foundation, VisareNorr, Norrbotten's local health authorities, and U.S. National Institute of Allergy and Infectious Disease (AI-20565 and AI-34607). GlaxoSmithKline World Wide Epidemiology, ALK and Phadia provided additional financial support.

Abbreviations

CI: confidence interval; ISAAC: International Study of Allergy and Asthma in Children; IgE: immunoglobulin E; OLIN: Obstructive Lung Disease in Northern Sweden; OR: odds ratio; RR: risk ratio; RS: respiratory syncytial virus; SPSS: Statistical Package for Social Sciences; SPT: skin prick test.

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Figure 1. Increase in allergic sensitization from 1996 to 2006 expressed as odds ratios

Footnote: Analysed by multiple logistic regression analyses including the variables sex, family history of allergy, number of siblings, rural living, living at a farm, and living within 200 m from a heavy traffic road as covariates.

Figure 2. Number of positive tests among sensitized children in 1996 and 2006

Footnote: Differences between number of positive tests in 1996 and 2006 calculated by One-Way ANOVA.

Figure 3. International trends in allergic sensitization in children

Table 1
Prevalence (%) of positive skin prick test in 1996 and 2006 by sex.

Allergen	1996 (n=2148)				2006 (n=1700)			
	Girls	boys	all	Diff by sex	Girls	Boys	all	Diff by sex
Birch	6.7	9.2	7.9	0.036	11.9	14.2	13.1	0.170
Timothy	5.2	8.1	6.7	0.007	8.7	13.1	10.9	0.004
Mugworth	0.8	1.0	0.9	0.649	2.6	2.2	2.4	0.592
Any pollen	10.3	14.4	12.3	0.004	16.7	19.8	18.3	0.098
Cat	12.2	14.6	13.4	0.107	17.7	20.5	19.1	0.139
Dog	8.1	9.3	8.7	0.343	12.9	18.5	15.7	0.001
Horse	4.8	7.4	6.1	0.011	8.0	10.0	9.0	0.159
Any animal	15.5	17.1	16.2	0.306	20.5	25.8	23.2	0.011
D. pteronyssinus	0.2	0.8	0.5	0.033	0.8	1.9	1.4	0.066
D. farinae	0	1.3	0.7	<0.001	0.4	1.3	0.8	0.035
Any mite	0.2	1.7	0.9	<0.001	0.8	2.0	1.4	0.045
Cladosporium	0.7	1.5	1.1	0.096	0.6	2.0	1.3	0.011
Alternaria	0.3	0.9	0.6	0.078	0.5	0.9	0.7	0.259
Any mould	0.8	1.9	1.4	0.037	0.8	2.4	1.6	0.013
Any allergen	19.0	22.3	20.6	0.059	27.2	32.6	29.9	0.016
								<0.001

Table 2
Prevalence (%) of risk factors in 1996 and 2006. Risk ratio (RR (95%CI)) for any positive SPT in 1996 and 2006.

Risk factor	Prevalence of risk factors (%)			Risk for positive SPT (RR (95%CI))	
	1996	2006	Diff by year p-value	1996	2006
Sex, boy	50.0	50.4	0.763	1.17 (0.99–1.39)	1.29 (1.05–1.59)
Family history of allergy	45.4	48.7	0.040	1.77 (1.43–2.19)	1.82 (1.47–2.24)
Number of siblings					
0	6.1	7.1	<0.001	1	1
1	42.2	50.2		0.73 (0.48–1.11)	0.95 (0.63–1.45)
2 or more	51.6	42.7		0.64 (0.42–0.97)	1.00 (0.65–1.52)
Mother smoking	31.8	15.5	<0.001	0.85 (0.68–1.07)	0.93 (0.69–1.25)
Dampness at home	20.8	12.3	<0.001	1.02 (0.78–1.31)	0.97 (0.71–1.35)
Any respiratory infection	58.4	28.1	<0.001	1.00 (0.84–1.19)	1.03 (0.88–1.22)
Infection of pertussis	44.6	2.4	<0.001	0.99 (0.84–1.17)	1.07 (0.68–1.68)
Breast feeding<3months	14.6	9.5	<0.001	0.97 (0.92–1.03)	1.07 (0.75–1.54)
Rural living at age 7/8y	12.4	10.8	0.117	0.57 (0.39–0.82)	0.77 (0.54–1.10)
Rural living first year of life	26.6	28.2	0.309	0.75 (0.58–0.96)	0.99 (0.79–1.27)
Ever living on a farm	2.7	2.5	0.703	0.28 (0.10–0.78)	0.63 (0.30–1.34)
Traffic road within 200m	44.1	42.2	0.235	1.09 (0.88–1.36)	1.27 (1.03–1.58)
Cat ever at home	26.5	24.4	0.143	0.58 (0.45–0.76)	0.49 (0.49–0.82)
Dog ever at home	33.8	36.1	0.142	0.69 (0.55–0.87)	0.66 (0.53–0.82)

Table 3**Table 3a. Risk factors, Odds ratio (OR95%CI), for sensitization to any allergen by multiple logistic regression analyses.**

Independent variables	Risk factors for a positive skin prick test (OR (95%CI))	
	Any Allergen	
	1996	2006
Male sex	1.25 (1.00–1.56)	1.30 (1.05–1.62)
Family history of allergy	1.80 (1.44–2.26)	1.70 (1.36–2.12)
Number of siblings		
0	1	1
1	0.62 (0.40–0.97)	0.88 (0.57–1.36)
≥ 2	0.54 (0.35–0.84)	0.96 (0.62–1.48)
Ever cat at home	0.66 (0.50–0.87)	0.70 (0.53–0.92)
Rural living	0.72 (0.49–1.05)	0.81 (0.56–1.19)
Ever living on a farm	0.29 (0.09–0.93)	0.88 (0.39–1.99)
Heavy traffic road 200m	1.03 (0.83–1.29)	1.28 (1.02–1.59)

Table 3a. Risk factors, Odds ratio (OR95%CI), for sensitization to any allergens from animal and pollen by multiple logistic regression analyses.

Independent variables	Risk factors for a positive skin prick test (OR (95%CI))			
	Any animal		Any pollen	
	1996	2006	1996	2006
Male sex	1.14 (0.90–1.45)	1.36 (1.07–1.72)	1.56 (1.18–2.05)	1.27 (0.98–1.64)
Family history of allergy	1.70 (1.33–2.17)	1.70 (1.34–2.17)	2.26 (1.70–3.01)	1.56 (1.20–2.03)
Number of siblings				
0	1	1	1	1
1 ≥	0.61 (0.38–0.99)	0.62 (0.40–0.97)	0.48 (0.29–0.80)	1.01 (0.60–1.71)
2	0.52 (0.33–0.83)	0.67 (0.43–1.06)	0.46 (0.27–0.76)	0.91 (0.54–1.56)
Ever cat at home	0.58 (0.43–0.80)	0.64 (0.48–0.87)	0.76 (0.54–1.07)	0.63 (0.45–0.88)
Rural living	0.69 (0.45–1.06)	0.80 (0.52–1.22)	0.82 (0.51–1.30)	0.86 (0.54–1.36)
Ever living on a farm	0.40 (0.12–1.30)	0.91 (0.36–2.26)	0.16 (0.02–1.17)	1.22 (0.48–3.05)
Heavy traffic road 200m	0.98 (0.77–1.26)	1.23 (0.97–1.56)	0.94 (0.71–1.24)	1.28 (0.98–1.66)

Table 4
Association (odds ratio and 95% CI) between sibling, respiratory infection and rural living, respectively, and different condition categories in 1996 and 2006 respectively.

		Condition categories (OR(95%CI))			
		No sensitization	No sensitization	Sensitization	Sensitization
		No asthma	Asthma	No asthma	Asthma
		(n=1635) [*]	(n=70) [*]	(n=375) [*]	(n=68) [*]
		(n=1134) ^{**}	(n=53) ^{**}	(n=437) ^{**}	(n=69) ^{**}
Any sibling	1996	1 (reference)	1.35 (0.42–4.38)	0.79 (0.50–1.24)	0.40 (0.19–0.83)
	2006	1 (reference)	0.92 (0.32–2.61)	1.22 (0.79–1.95)	0.39 (0.20–0.77)
Any respiratory infection	1996	1 (reference)	4.01 (2.09–7.69)	0.95 (0.76–1.20)	1.88 (1.09–3.23)
	2006	1 (reference)	4.79 (2.71–8.49)	0.96 (0.73–1.25)	2.91 (1.76–4.79)
Rural living	1996	1 (reference)	0.94 (0.46–1.93)	0.62 (0.42–0.91)	0.30 (0.09–0.95)
	2006	1 (reference)	0.99 (0.41–2.35)	0.78 (0.54–1.13)	0.74 (0.31–1.73)

* number of children in each category in 1996
** number of children in each category in 2006. Complete SPT and questionnaire data was available for 1693 children.

Prevalence (%) of ever having had respiratory infections by number of siblings reported in 1996 and 2006, respectively, among 7–8 year old children.

Table E1

	Number of siblings				All	Diff by siblings [*]	Diff by siblings ^{**}	Diff by year
	0	1	≥2					
Croup								
	1996	10.6	13.8	14.3	13.9	0.390	0.185	0.015
	2006	11.4	17.1	15.6	16.1	0.127	0.074	
Pneumonia								
	1996	16.1	20.2	17.3	18.4	0.082	0.406	<0.001
	2006	13.0	11.3	10.9	11.3	0.704	0.435	
RS virus								
	1996	2.8	1.1	1.4	1.3	0.152	0.072	<0.001
	2006	3.3	2.7	3.4	3.0	0.647	0.865	
Pertussis								
	1996	40.0	46.4	43.8	44.6	0.145	0.190	<0.001
	2006	1.1	2.4	2.6	2.4	0.448	0.317	
Croup, pneumonia or RS virus								
	1996	26.1	30.9	27.5	28.8	0.077	0.400	<0.063
	2006	24.5	27.0	26.4	26.6	0.755	0.503	
Any respiratory infection								
	1996	56.7	61.0	58.6	58.4	0.052	0.582	<0.001
	2006	25.0	28.9	27.6	28.1	0.509	0.340	

* p-value by Chi-square test or Fisher's exact test; no sibling versus any sibling

** p-value by ANOVA test for trend

Table E2

Proportion of children with a positive skin prick test (SPT) and specific IgE $\geq$ 0.35 I.U./ml, respectively, in the validation study by negative and positive SPT in the main SPT study in 2006.

Positive and negative SPT in the main study	Results in the validation study	
	Positive SPT	IgE $\geq$ 0.35
Positive		
Cat	38/40 (95.0%)	28/34 (82.4%)
Dog	25/32 (78.1%)	21/27 (77.8%)
Horse	18/21 (85.7%)	13/16 (81.3%)
Birch	29/32 (90.6%)	24/25 (96%)
Timothy	19/19 (100%)	15/16 (93.8%)
D. pteronyssinus	1/1 (100%)	-
D. farinae	1/1 (100%)	-
Cladosporium	3/3 (100%)	-
Alternaria	1/1 (100%)	-
Any allergen	56/59 (94.9%)	43/50 (86.0%)
Negative		
Cat	2/19 (10.5%)	1/16 (6.3%)
Dog	1/27 (3.7%)	6/23 (26.1%)
Horse	0/38 (0%)	5/33 (15.2%)
Birch	6/27 (22.2%)	5/24 (20.8%)
Timothy	3/40 (7.5%)	3/33 (9.1%)
D. pteronyssinus	0/55 (0%)	-
D. farinae	0/55 (0%)	-
Cladosporium	0/53 (0%)	-
Alternaria	1/55 (1.8%)	-