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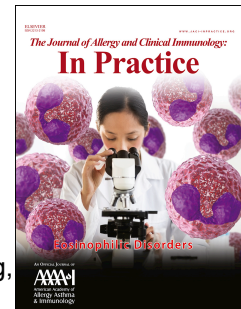
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The majority of children sensitized before school-age develop allergic disease before adulthood: a longitudinal population-based study

Joakim Bunne, MD¹, Linnea Hedman, PhD¹, Matthew Perzanowski, PhD², Anders Bjerg, MD, PhD³, Anna Winberg, MD, PhD⁴, Martin Andersson, MD, PhD¹, Bo Lundbäck, MD, PhD⁵, Thomas Platts-Mills, MD, PhD⁶, and Eva Rönmark, PhD¹

¹Department of Public Health and Clinical Medicine, Division of Sustainable Health, the OLIN unit, Umeå University, Umeå, Sweden

²Department of Environmental Health Sciences, Mailman School of Public Health, Columbia University, New York, NY, USA.

³Department of Women's and Children's Health, Karolinska Institutet, Stockholm, Sweden

⁴Department of Clinical Sciences, Pediatrics, Umeå University, Sweden

⁵Krefting Research Centre, Institute of Medicine, University of Gothenburg, Gothenburg, Sweden

⁶Division of Allergy & Clinical Immunology, University of Virginia, Charlottesville, VA, USA.

Correspondence:

Eva Rönmark, PhD, Professor

E-mail address: eva.ronmark@norrbottn.se

Telephone: +46 70 542 4431

Postal address: Department of Public Health and Clinical Medicine, Division of Sustainable health/the OLIN Unit, Umeå University, Umeå, Sweden

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50 **e-mail to all authors:**

51 joakim.bunne@gmail.com; linnea.hedman@norrboten.se; mp2217@cumc.columbia.edu ;

52 bjerg.anders@gmail.com; anna.winberg@umu.se; martin.andersson@umu.se; bo.lundback@gu.se;

53 tap2z@virginia.edu; eva.ronmark@nll.se

ABSTRACT

Background: Allergic sensitization increases the risk of asthma and allergic rhinitis, but the impact of age at onset of sensitization is less studied.

Objective: To examine the cumulative incidence of asthma and rhinitis up to age 19 years in relation to age at onset of sensitization to airborne allergens.

Method: All children in grade one and two (median age 8 years) in two municipalities in Northern Sweden were invited to skin prick tests and a questionnaire about allergic diseases, and 88% participated. At ages 12 and 19 years the protocol was repeated, and n=1510 individuals participated in all three examinations. Specific IgE was collected in a random sample at age 19, n=770. Onset of sensitization was defined; ≤ 8 years, 8-12 years, 12-19 years, and never sensitized. Adjusted Poisson regression was utilized to calculate risk ratios.

Results: At age 19, those sensitized ≤ 8 year had the highest risk of asthma (RR 4.68 (95%CI 3.14-6.97)) and rhinitis (RR 22.3 (95%CI 13.3-37.6)), and 84% had developed either asthma or rhinitis. The combination of sensitization ≤ 8 year and family history of allergic diseases rendered high risks for asthma (RR 10.6 (6.71-16.7)) and rhinitis (RR 36.3 (18.9-69.7)). Individuals sensitized ≤ 8 year showed significantly highest level of sensitization, as judged by number of positive skin tests and titers of specific IgE.

Conclusion: The majority of individuals with sensitization ≤ 8 years developed asthma or rhinitis before young adulthood. The high level of sensitization in early sensitized contribute to the high incidence of allergic airway conditions.

Highlights box

- *What is already known about this topic?* Allergic sensitization is a well-known risk factor for asthma and rhinitis, but the importance of age at first sensitization to airborne allergens is less described.
- *What does this article add to our knowledge?* This longitudinal study illustrates that the earlier onset of sensitization occur, the higher the risk of developing asthma and/or rhinitis. We identified an “allergy cluster” defined by early sensitization, high levels of sensitization and a very high risk of allergic disease.
- *How does this study impact current management guidelines?* Attention to symptoms of asthma and rhinitis are warranted in children sensitized before school age, as they rarely remain asymptomatic until adolescence, and early diagnosis of allergy is essential for interventions and treatment.

Key words: Allergic sensitization, asthma, rhinitis, longitudinal study, epidemiology

Abbreviations

CI - Confidence Interval

IgE - Immuno globuline E

ISAAC - International Study of Asthma and Allergy In Children

I.U - International Unit

OLIN - The Obstructive Lung Disease In Northern Sweden

RR - Risk Ratio

SPT - Skin Prick Test

INTRODUCTION

Asthma and rhinitis are global public health concerns and in high income countries they are the most common diseases in childhood and young adulthood (1,2). They frequently occur together, but while most people affected by asthma also have rhinitis, a large proportion of individuals with rhinitis do not have asthma (3,4). Longitudinal studies have demonstrated that aeroallergen sensitization in childhood is strongly associated with the development of asthma and rhinitis during childhood and teenage (5-8). Preschool sensitization is also a risk factor for asthma persistence during adolescence (9). In addition, allergic sensitization has been strongly associated with early onset of asthma among adults with asthma (10). While a strong association has been shown between titers of specific IgE antibodies to airborne allergens and prevalence as well as severity of asthma (11), the strength of association between allergic sensitization and rhinitis is even more pronounced (5,10,12-16).

The prevalence of allergic sensitization increases with age, peaking in young adulthood with sensitization rates to airborne allergens reaching up to 50 % of the population in some areas (17-21). The high prevalence of sensitization in young adulthood is a result of high incidence and low remission during childhood and adolescence (17,18,20). Despite a strong association between IgE sensitization and clinical symptoms from the airways, asthma and rhinitis may occur without allergic sensitization and vice versa (12,14,16-24). Independently of allergic sensitization, onset of allergy symptoms can be influenced by a number of intrinsic and environmental factors, including a genetic predisposition (1,2,22-25). Even though this is a well-researched area, there is still a lack of longitudinal studies investigating the significance of age at onset of aeroallergen sensitization in relation to development of airway symptoms up to young adulthood.

The primary aim of this study was to examine the impact of age at onset of sensitization to airborne allergens on the development of asthma and rhinitis during childhood and adolescence. A secondary aim was to examine to what extent individuals sensitized to airborne allergens remain free from symptoms of asthma and rhinitis in a longitudinal perspective up to 19 years of age.

METHODS

Study population

In 1996, within the research program Obstructive Lung diseases in Northern Sweden (OLIN) studies, a population-based cohort of schoolchildren was invited to a questionnaire survey about allergic diseases (22). All children in first and second grade, 7-8 years of age (median 8 years), in three municipalities of northern Sweden were invited to the study. From first grade, school is mandatory in Sweden. All children in two of the municipalities were also invited to skin prick testing (SPT) for common airborne allergens (22,23). The cohort was re-examined at 11-12 (median 12) years and 19 years of age (11,20,26,27). At recruitment, participation in the questionnaire was 97%, and 88 % (n=2148) participated in SPT. This paper is based on the 1510 individuals (70% of the participants at age 8 years) that participated in SPT at all three examinations. At age 19 years, at the same occasion as the SPT test, a random sample of the cohort had their blood drawn for serum studies (n=770) (10). The studies were approved by the Regional Ethical Review Board in Umeå, Sweden. The parents and/or the participants gave informed consent.

Questionnaire

The questionnaire was based on the International Study of Asthma and Allergy in Childhood (ISAAC) questionnaire (28), but included additional questions about physician diagnoses, use of medication, symptoms and risk factors for allergic sensitization, asthma, and allergic rhinitis (22,29). The questions regarding symptoms and diseases were identical in the three surveys. The first two questionnaires were distributed by the schools and completed by the caregivers, predominantly mothers, while the survey at age 19 years was completed by the participants themselves. The question about physician diagnosed asthma has been validated and showed high specificity (23), and the agreement between the answers given by the parents and the children for questions regarding asthma and rhinitis was excellent (30).

Allergic sensitization

The SPTs were performed at the schools and by a limited number of specifically trained staff during February to April at all examinations, and in line with the European Academy of Allergy and Clinical Immunology (EAACI) recommendations (31). The test panel included ten common airborne allergens; birch, timothy, mugwort, dog, cat, horse, *Dermatophagoides farinae*, *D pteronyssinus*, *Cladosporium herbarum* and *Alternaria alternata* (Soluprick, ALK, Hørsholm, Denmark). Histamine 10 mg/mL and glycerol were used as positive and negative controls, respectively. The tests were performed on the volar part of the forearm using 1 mm tip lancets. A positive reaction was defined as a wheal diameter ≥ 3 mm after 15 minutes. The SPTs have been validated against specific IgE in serum with good agreement (7,14,26,27). For the current study, serum was available for 770 randomly selected individuals at age 19 years and analyses of specific IgE to cat, dog, horse, birch, and timothy were performed by commercially available ImmunoCAP provided by ThermoFisher Scientific (11). The detection level for serum IgE was 0.35 I.U./ml and levels below that was set to 0.18 I.U./ml.

Definitions

The main definitions are presented below and a complete list of definitions is presented in Table E1. The definition of age at onset of sensitization was based on the three time points of SPT of the cohort and corresponds to sensitization to any allergen, any animal, any pollen and a specific allergen.

≤ 8 years: First time of reading a positive SPT was at age 8 years, i.e. development of sensitization occurred ≤ 8 years.

8-12 years: First time of reading a positive SPT was at age 12 years, i.e. development of sensitization occurred between 8 and 12 years.

12-19 years: First time of reading a positive SPT was at age 19 years, i.e. development of sensitization occurred between 12 and 19 years.

Never: Negative SPT at all ages.

The main outcomes were *current wheeze, current asthma, current symptoms of rhinitis, and current rhinitis*.

Statistical analysis

Analyses were performed using IBM SPSS Statistics, Version 26.0. (IBM Corp. Armonk, NY, NY).

Differences in proportions between two groups were analysed by chi-square test, and by Mantel-

Haentzel tests for more than two groups. The differences in geometric mean levels of specific IgE,

and the sum of the IgE titers to the major specific IgE (cat, dog, horse, birch and timothy) at age 19

years by age at onset of a positive SPT was analysed by Kruskal Wallis non-parametric test.

Significance was defined as a p-value <0.05. The associations between asthma and rhinitis at age 19

years and age at onset of allergic sensitization were calculated using Poisson regression analyses and

expressed as risk ratios (RR) with 95 % confidence intervals (CI). Dependent variables were: current

wheeze, current asthma, current symptoms of rhinitis, and current rhinitis. Covariates included in the

models were sex, family history of asthma or rhinitis, urban vs rural living at age 8, having a smoking

mother at age 8, ever having pets at home at age 8, and age at onset of allergic sensitization with

never sensitized as reference. The *cumulative incidence* was defined as report of the condition at a

specific age or in any of the previous surveys. For analyses of the combined effect of age at onset of

allergic sensitization and family history of asthma and rhinitis, respectively, on the cumulative

incidence of asthma and rhinitis at age 19 years, eight mutually exclusive categories based on age at

onset of allergic sensitization and on family history of asthma (rhinitis) were created, using those

never sensitized with no family history of asthma (rhinitis) as reference category, and included in a

Poisson model as presented above.

RESULTS

Prevalence of asthma, rhinitis and allergic sensitization by age

The prevalence of all outcomes increased by age and was highest at age 19 years; *current wheeze* 15.4 %, *current asthma* 10.9 %, *current symptoms of rhinitis* 28.3%, and *current rhinitis* 13.4 %. For most outcomes the prevalence was higher among boys than girls at early ages, but at age 19 years, an opposite pattern or no difference by sex was found (Figure 1, Table E2).

The prevalence of *any positive SPT* increased by age, from 21.4 % at age 8, to 31.1 % (age 12) and 43.0 % (age 19 years), and was significantly more common among boys than girls at all examinations (Figure 1, Table E2). The same pattern was found for sensitization to *any animal* and *any pollen* (Figure 1). A low prevalence of positive SPT to mite and mould was found at all ages, 1.1-1.5 % at age 8 years, and 2.4-3.8% at age 19 years (data not in figure). Of the 1510 individuals participating in the study, 323 (21%) had developed sensitization at age ≤ 8 years, 160 (11%) between 8-12 years, and 184 (12%) between 12-19 years, while 843 (56%) were never sensitized.

Asthma and rhinitis in relation to age at onset of allergic sensitization

At age 19, the prevalence of all outcomes was highest among those sensitized ≤ 8 years, declined by increasing age at onset of sensitization, and was lowest among never sensitized. The relationships between outcomes and age at onset of sensitization were similar for sensitization to any allergen, any animal and any pollen and the patterns were similar for boys and girls (Table 1, Table E3).

The association between age at onset of sensitization and asthma and rhinitis, respectively, at age 19 years remained after adjustment for covariates. In general, allergic sensitization had a stronger association with outcomes of rhinitis than outcomes of asthma. The RR for *current rhinitis* at age 19 years was 22.3 (95 % CI 13.3-37.6) for those sensitized ≤ 8 years vs never sensitized to any allergen.

Corresponding RR for *current asthma* was 4.68 (95 % CI 3.15-6.97) (Table 2). The pattern was similar among girls and boys (Table E4 and E5)

Sensitization ≤ 8 years to any pollen and any animal were both strongly associated with rhinitis, with higher RRs for pollen. The RR for *current rhinitis* at age 19 years was 20.5 (95 % CI 13.3-31.6) for sensitized ≤ 8 years vs never sensitized to any pollen, and RR 12.1 (95 % CI 8.15-18.0) for sensitized ≤ 8 years vs never sensitized to any animal. For the asthma variables, the associations with sensitization to any pollen and any animal were of similar strength, RR 3-4 for sensitized ≤ 8 years vs never sensitized to any pollen and any animal, respectively (Table 2). The pattern was similar among girls and boys (Table E4 and E5).

During the study period, 42.1 % reported *current wheeze* at any survey up to age 19 years (cumulative incidence) among those sensitized ≤ 8 years compared with 16.4 % among never sensitized. For *current asthma*, the corresponding percentages were 30.7 % and 6.3 %, respectively (Figure 2). The cumulative incidence of *current symptoms of rhinitis* at age 19 was 76.2 % among those sensitized ≤ 8 years vs 23.5 % among never sensitized. The corresponding figures for *current rhinitis* were 56.7 % among sensitized ≤ 8 years vs 3.3 % among never sensitized (Figure 3). At age 19 years, 84.2 % of those sensitized ≤ 8 years had reported symptoms or diagnosis of asthma or rhinitis in any of the surveys, thus 15.8% remained free from symptoms of asthma and rhinitis.

The combined effect of age at onset of sensitization and family history of allergic disease

The cumulative incidence of asthma and rhinitis up to age 19 years was highest among those with both a family history and onset of allergic sensitization to any allergen before the age of 8 years. The effect of allergic sensitization was generally stronger than a family history of the disease. Sensitized ≤ 8 years with a family history of rhinitis, compared with never sensitized without family history, yielded very high RR for *current rhinitis*, 36.3 (95 % CI 18.9-69.7). Corresponding RR for *current asthma* was 10.6 (6.71-16.7) (Table 3).

The level of sensitization judged by number of positive SPT and by the titers of specific IgE

At age 19 years, 66% of individuals who developed their sensitization ≤ 8 years had ≥ 4 positive SPT reactions, compared with 9.2% among those sensitized between 12-19 years ($p < 0.001$) (Figure 4 a). Also, at first time of reading a positive SPT, multi-sensitization was more common among those sensitized ≤ 8 years than those who had developed sensitization later (Figure 4 b). At age 19 years, the cumulative titer of IgE antibodies to the five allergens analysed (cat, dog, horse, birch and timothy) was significantly higher among those early sensitized (geometric mean 30.0) compared with those sensitized between 12-19 years (3.21). The same pattern was found for each of the individual allergens (Table 4).

DISCUSSION

In this population-based study following a cohort of children from 8 to 19 years of age, age at onset of allergic sensitization to aeroallergens was important for the risk of development of asthma and rhinitis. The risk was consistently highest for those who were sensitized before the age of 8, independent of sex and family history of allergic disease. In addition, children with early sensitization had higher levels of specific IgE to aeroallergens at 19 years of age and were more often sensitized to multiple allergens compared to children first found to be sensitized at the pre-teenage or teenage stage. Finally, the majority of children sensitized before age 8 years had experienced symptoms of asthma or rhinitis by age 19.

There are a number of possible contributing factors to why individuals with early sensitization were at such high risk of developing clinical symptoms until young adulthood. A long duration of sensitization increases the risk of developing high levels of specific IgE, molecular spreading and multi-sensitization, all of them associated with both asthma and rhinitis (11,17,19,20,26). Also, longer time at risk when being sensitized, the higher the risk of developing clinical symptoms (11,19). Concordantly, at age 19 years (study endpoint) those who were early sensitized had higher specific IgE levels and were more often multi-sensitized than those who developed sensitization later.

Notably, as presented in figure 4b, sensitization to multiple allergens also at first time of reading a positive SPT was more common among those with early sensitization compared with individuals first found to be sensitized at the pre-teen or teenage stage. This suggests a more rapid progress of sensitisation among early sensitized. Our results are in line with a British birth cohort with follow-ups up to the age of 8, which found the “early multiple sensitization cluster” most strongly associated with asthma (32). Also, a Danish longitudinal study investigating IgE sensitization to 22 food and aeroallergens in a cohort between 6 months and 13 years of age found that multi-sensitization, increasing specific IgE levels and persistent sensitization during childhood were associated with

increased risk of asthma at age 13 years (33). Similarly, a German multicentre study showed an association between early sensitization and asthma at 7 years of age (34). This is in accordance with the thesis that the conditions required for an “atopic march” from sensitization to persistent allergy symptoms are often set very early in life (35). Thus, it seems that those highly genetically predisposed for allergy are sensitized early in life, contributing to the high incidence of clinical symptoms in this group also until young adulthood.

Even though we know that genetic predisposition for allergic diseases, sex, early onset eczema and environmental factors like allergen exposure, number of siblings and the microbial setting surrounding the child compose important factors for health and disease (1,2,7,22,27,36-38), we are still far from understanding the complex enigma of allergy and tolerance development. Future studies including genetics and stratification by age of onset of allergic sensitization may identify an allergy-prone genotype that could better clarify the process of developing allergic diseases.

Cross-sectional analyses based on the cohort showed a strong association between sensitization to airborne allergens and asthma already at the age of 8 years (14,22), results in line with well-known findings (16,39). In the longitudinal setting, the cumulative incidence of asthma and rhinitis continued to increase by age, and at 19 years the prevalence of these conditions was by far the highest among those early sensitized. The development of allergic disease among those not sensitized at 8 years was highly dependent on the development of sensitization in the subsequent years. For those who developed sensitization between 8 and 12 years, the cumulative incidence of asthma and rhinitis at 12 years increased considerably by the age of 19 years. For those who developed sensitization between 12 and 19 years, the cumulative incidence of asthma and rhinitis at age 8 and 12 years was similar to those never sensitized, but had increased markedly at age 19 years. The association between sensitization and symptoms was stronger for rhinitis than for asthma, which is in accordance with other studies (10, 40,41). In line with findings from the few available longitudinal cohort studies (5,7,33,34,42-44), the current study with three observation points clearly

illustrated the temporality of the associations between allergic sensitization and development of allergic diseases.

Based on cross sectional studies, it might be assumed that subjects may be sensitized to aeroallergens without experiencing clinical symptoms throughout life (12,16,22). However, a Swedish birth cohort study found that 77% of those sensitized to food or aeroallergens at any time during the follow-up reported asthma, rhinitis or eczema at any time up to the age of 16 years (5). In contrast to our study they also included eczema among the outcomes, and did not take age at sensitization into account. In our study 84% of those with early sensitization developed symptoms or diagnosis of asthma or rhinitis before until young adulthood. As the prevalence of allergic rhinitis peaks in early adulthood (10,44), a further incidence among the few remaining asymptomatic sensitized individuals can be expected.

In line with the findings of others (8,10,14,40), we found that sensitization to pollen was more strongly associated with rhinitis, while sensitization to animals tended to be strongly associated with asthma. However, the impact of age at onset of sensitization showed the same pattern for the two allergen groups. In accordance with previous data (4,10,22,23), having a family history of asthma and rhinitis was consistently associated with development of airway disease. The contribution of heredity to the risk of developing asthma and rhinitis was, however, not as strong as the contribution of preschool sensitization. This was especially evident for current rhinitis, reflected by a RR of 4.4 for those never sensitized but with a family history compared to RR 31 for those early sensitized without a family history and a RR of 40 for those with both early sensitization and a family history.

Sensitization to aeroallergens was more common among boys than girls at all three time-points. Despite this, reported symptoms of asthma and rhinitis were more common among girls than boys at 19 years of age. Others have reported a shift in the gender distribution of asthma during adolescence, as asthma tends to be more prevalent among boys than girls but also more prevalent among women than men (45-47). It has also been shown that adult onset asthma is more often non-

allergic compared to asthma with onset at younger ages (10,47). However, in the current study, the incidence of asthma and rhinitis among those never sensitized remained low during the entire observation period, and the effect of age at sensitization on clinical symptoms followed the same pattern among boys and girls.

The strengths of this study are the size of our study population, the very high participation rates, the longitudinal study design, and the representative sample (20). The 3 observation points during the 11-year study period allowed us to investigate the impact of age at sensitization on the association with the sometimes year-long process of developing clinical symptoms, an association that could be underestimated when using a cross-sectional study design. The ISAAC questionnaire has been extensively used and validated internationally (28), and also in our cohort (23,30). The SPTs were performed by a limited number of specifically trained staff at the same time of year using test extracts from the same at supplier at all surveys. Allergic sensitization was mainly assessed by SPT and SPT results in the cohort have been validated against specific IgE with good agreement (7,23,27), and the consistency of the skin prick test was high (20). In other studies assessing SPT versus IgE, good correlations between the measurements as well as associations with clinical symptoms has been reported (48). The prevalence of allergic sensitization and diseases are in level to other studies (5,16,17,45), assuring external validity. As the cohort was recruited at age 8 years, we are lacking data on allergic sensitization before age 8 years, which is a limitation of the study.

In conclusion, in this longitudinal cohort followed from age 8 to 19 years, we found that sensitization to aeroallergens before age 8 years was associated with a very high incidence of asthma and rhinitis from childhood to young adulthood. In fact early sensitization was associated with an “allergy cluster” defined by early sensitization, multi-sensitization, higher levels of sensitization and a very high risk of allergic disease, and this was independent of parental allergic disease.

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LEGENDS TO FIGURES

Figure 1. Prevalence (%) of asthma, rhinitis and allergic sensitization (positive skin prick test) by increasing age at examination.

Figure 2. Cumulative incidence (%) of current wheeze and current asthma, respectively, by increasing age and by age at onset of allergic sensitization.

*Current wheeze: "Has your child/Have you had wheezing or whistling in the chest in the last 12 months?"

**Current asthma: Physician-diagnosed asthma and either current wheeze or use of asthma medication in the last 12 months.

Figure 3. Cumulative incidence (%) of current symptoms of rhinitis and current rhinitis, respectively, by increasing age and by age at onset of allergic sensitization.

*Current symptoms of rhinitis: "In the last 12 months, has your child/have you had a problem with sneezing, or a runny, or a blocked nose when your child/you did not have a cold?"

**Current rhinitis: Physician-diagnosed allergic rhinitis and either current symptoms of rhinitis or use of medication for rhinitis in the last 12 months.

Figure 4. Proportion (%) of number of positive SPT at A) age 19 years by age at development of sensitization, and B) at age at first reading a positive SPT.

Table 1. Prevalence (%) of asthma and rhinitis at 19 years, by age at onset of allergic sensitization to any allergen among girls, boys and all.

Condition		Age at onset of sensitization				difference by age at onset, p-value
		Never n=843	12-19 years n=184	8-12 years n=160	≤ 8 years n=323	
Current wheeze	Girls	11.7	18.6	29.4	33.1	<0.001
	Boys	7.3	10.3	18.5	21.9	<0.001
	All	9.6	14.7	23.1	26.9	<0.001
Physician diagnosis of asthma	Girls	9.7	15.5	19.1	32.4	<0.001
	Boys	6.8	14.9	20.7	33.7	<0.001
	All	8.3	15.2	20.0	33.1	<0.001
Current asthma	Girls	6.3	13.4	17.6	26.9	<0.001
	Boys	3.3	9.2	14.1	21.9	<0.001
	All	4.9	11.4	15.6	24.1	<0.001
Current symptoms of rhinitis	Girls	16.0	43.3	61.8	69.0	<0.001
	Boys	8.3	24.1	41.3	45.5	<0.001
	All	12.3	34.2	50.0	56.0	<0.001
Physician diagnosis of rhinitis	Girls	1.8	8.2	36.8	48.3	<0.001
	Boys	2.0	8.0	29.3	43.3	<0.001
	All	1.9	8.2	32.5	45.5	<0.001
Current rhinitis	Girls	1.6	8.2	33.8	44.8	<0.001
	Boys	1.5	8.0	23.9	36.0	<0.001
	All	1.5	8.2	28.1	39.9	<0.001

Table 2. Risk for asthma and rhinitis at 19 years, by age at onset of allergic sensitization to any allergen, pollen and animal, respectively, by Poisson regression analyses and presented as Risk Ratios (RR) with 95% Confidence intervals (95%CI).

Type of sensitization	Age at onset of sensitization	Dependent variables			
		Current Wheeze	Current asthma	Current symptoms of rhinitis	Current rhinitis
Any SPT	≤ 8 years	2.79 (2.04-3.81)	4.68 (3.15-6.97)	4.58 (3.57-5.87)	22.3 (13.3-37.6)
	8-12 years	2.45 (1.64-3.66)	3.14 (1.87-5.27)	4.23 (3.14-5.70)	16.6 (9.40-29.1)
	12-19 years	1.51 (0.97-2.35)	2.31 (1.35-3.95)	2.74 (1.99-3.76)	3.86 (1.88-7.93)
	Never	1	1	1	1
Any animal	≤ 8 years	2.86 (2.11-3.87)	4.45 (3.11-6.39)	8.33 (5.99-11.6)	12.1 (8.15-18.0)
	8-12 years	2.23 (1.45-3.45)	2.52 (1.46-4.36)	9.03 (6.17-13.2)	10.1 (6.37-16.1)
	12-19 years	1.23 (0.76-1.99)	1.51 (0.84-2.72)	6.68 (4.59-9.70)	7.30 (4.61-11.6)
	Never	1	1	1	1
Any pollen	≤ 8 years	2.68 (1.02-3.76)	3.47 (2.32-5.18)	10.0 (7.21-13.9)	20.5 (13.3-31.6)
	8-12 years	2.26 (1.53-3.33)	3.15 (2.00-4.96)	8.06 (5.66-11.5)	16.1 (10.2-25.4)
	12-19 years	1.81 (1.23-2.67)	2.41 (1.53-3.80)	4.22 (2.84-6.27)	3.63 (1.99-6.63)
	Never	1	1	1	1

Adjusted for sex, family history of condition (asthma or allergic rhinitis, respectively), rural/urban living, any furry animal at home, and having a smoking mother at age 8
SPT: skin prick test

Table 3. Cumulative incidence (%) of asthma (A) and rhinitis (B) at 19 years by age at onset of allergic sensitization to any allergen and family history. Risk ratio (RR) with 95 % confidence intervals (95%CI) analysed by Poisson regression analyses

(A)	Age at onset of sensitization	Family history of asthma (n)	Current wheeze		Current asthma	
			Incidence, %	RR (95 % CI)*	Incidence, %	RR (95 % CI)*
Never		No (725)	14.5	1	5.0	1
		Yes (118)	28.0	1.94 (1.30-2.91)	14.4	2.86 (1.58-5.18)
12-19 years		No (145)	20.7	1.51 (1.00-2.28)	11.0	2.33 (1.28-4.22)
		Yes (39)	30.8	2.22 (1.22-4.04)	20.5	4.34 (2.00-9.40)
8-12 years		No (129)	28.7	2.09 (1.42-3.06)	15.5	3.27 (1.88-5.69)
		Yes (31)	48.4	3.53 (2.01-6.19)	45.2	8.67 (4.48-16.8)
≤ 8 years		No (243)	35.4	2.58 (1.92-3.46)	22.6	4.61 (2.98-7.14)
		Yes (80)	62.5	4.36 (3.08-6.18)	55.0	10.6 (6.71-16.7)

(B)	Age at onset of sensitization	Family history of rhinitis (n)	Current symptoms of rhinitis		Current rhinitis	
			Incidence, %	RR (95 % CI)*	Incidence, %	RR (95 % CI)*
Never		No (570)	20.0	1	1.6	1
		Yes (273)	30.8	1.55 (1.16-2.07)	7.0	4.90 (2.34-10.2)
12-19 years		No (109)	36.7	1.85 (1.28-2.66)	7.3	4.09 (1.62-10.4)
		Yes (75)	57.3	2.97 (2.08-4.23)	18.7	10.9 (4.89-24.3)
8-12 years		No (95)	58.9	3.00 (2.17-4.16)	28.4	18.7 (9.18-38.0)
		Yes (65)	63.1	3.37 (2.33-4.87)	38.5	25.8 (12.5-53.0)
≤ 8 years		No (173)	71.7	3.63 (2.79-4.73)	50.9	31.0 (16.1-59.5)
		Yes (150)	81.3	4.22 (3.25-5.48)	63.3	36.3 (18.9-69.7)

*Adjusted for sex, rural/urban living, any furry animal at home, and having a smoking mother at age 8.

Table 4. Levels of specific IgE at age 19 years expressed in geometric means and percentiles (25% and 75%) by age at onset of sensitization as measured by skin prick test

	Age at onset of positive SPT to any allergen			p-value [‡]
	12-19 years	8-12 years	≤ 8 years	
Sum of IgE [#]	3.21 (0.90; 12.02)	9.44 (3.40; 28.42)	30.02 (11.37; 83.85)	<0.001
	Age at onset of positive SPT to the specific allergen			p-value [‡]
	12-19 years	8-12 years	≤ 8 years	
Specific IgE to cat	1.44 (0.18; 7.71)	2.37 (0.18; 8.08)	4.93 (1.12; 19.2)	0.001
Specific IgE to dog	0.27 (0.18; 0.18)	0.29 (0.18; 0.18)	1.10 (0.18; 3.30)	<0.001
Specific IgE to horse	0.89 (0.18; 2.98)	2.02 (0.62; 8.94)	4.88 (0.63; 26.9)	0.001
Specific IgE to birch	1.48 (0.41; 5.03)	4.75 (1.23; 17.2)	20.7 (8.81; 64.2)	<0.001
Specific IgE to timothy	1.11 (0.18; 5.51)	4.03 (0.82; 21.4)	17.6 (7.89; 45.5)	<0.001

The lowest level of detection of IgE antibody was 0.35 I.U/ml and levels below that was given a value of 0.18 I.U/ml.

[#] Sum of specific IgE to cat, dog, horse, birch and timothy

[‡] Differences by groups analysed by Kruskal Wallis test

Table E1. Definitions of allergic sensitization, outcomes of asthma and rhinitis, and covariates included in adjusted models.

Allergic sensitization	
Any positive SPT	A positive reaction (≥ 3 mm) to any of the ten tested allergens (birch, timothy, mugwort, dog, cat, horse, <i>Dermatophagoides farinae</i> , <i>D pteronyssinus</i> , <i>Cladosporium herbarum</i> or <i>Alternaria alternata</i>)
Any animal	A positive reaction to cat, dog or horse
Any pollen	A positive reaction to birch, timothy or mugwort
Outcomes of asthma and allergic rhinitis	
Current wheeze	Has your child/Have you had wheezing or whistling in the chest in the last 12 months?
Physician-diagnosed asthma	Has your child/Have you been diagnosed as having asthma by a physician?
Current asthma	<i>Physician-diagnosed asthma</i> and either <i>current wheeze</i> or use of asthma medication in the last 12 months.
Current symptoms of rhinitis	In the last 12 months, has your child/have you had a problem with sneezing, or a runny, or a blocked nose when your child/you did not have a cold?
Physician-diagnosed rhinitis	Has your child/Have you been diagnosed as having hay fever or allergic nose or eye problems by a physician?
Current rhinitis	<i>Physician-diagnosed allergic rhinitis</i> and either <i>current symptoms of rhinitis</i> or use of medication for rhinitis in the last 12 months.
The outcomes are presented as prevalence at different ages and also as cumulative incidence during the observation period.	
Cumulative incidence	A report of the condition at a specific age or in any of the previous surveys.
Covariates included in the adjusted models	
Family history of asthma	Mother or father with a history of asthma.
Family history of rhinitis	Mother or father with a history of allergic nose or eye conditions
Smoking mother	Mother was a current smoker as reported at age 8 years
Pets at home	Ever having had cat or dog at home as reported at age 8 years
Urban/rural living	Current living at age 8 years
Missing data	The number of missing data was very low. Missing in questions on symptoms and diseases was treated as no, while missing in exposures was treated as missing

Table E2. Prevalence (%) of asthma, rhinitis, and allergic sensitization by sex and increasing age

Outcome		Girls n=755	Boys n=755	All n=1510	Difference by sex, p-value
Current wheeze	8 years	9.5	11.8	10.7	0.156
	12 years	6.6	8.7	7.7	0.122
	19 years	18.3	12.5	15.4	0.002
Physician diagnosis of asthma	8 years	5.0	7.7	6.4	0.035
	12 years	7.5	9.7	8.6	0.142
	19 years	15.6	15.8	15.7	0.944
Current asthma	8 years	4.6	6.9	5.8	0.060
	12 years	5.8	7.8	6.8	0.126
	19 years	12.2	9.7	10.9	0.117
Current symptoms of rhinitis	8 years	13.2	17.9	15.6	0.013
	12 years	17.7	21.9	19.8	0.045
	19 years	33.8	22.9	28.3	<0.001
Physician diagnosis of rhinitis	8 years	5.8	9.8	7.8	0.004
	12 years	9.9	14.4	12.2	0.007
	19 years	14.7	15.8	15.2	0.567
Current rhinitis	8 years	5.2	8.3	6.8	0.014
	12 years	7.0	11.8	9.4	0.002
	19 years	13.6	13.1	13.4	0.762
Any positive SPT	8 years	19.2	23.6	21.4	0.038
	12 years	27.2	35.0	31.1	<0.001
	19 years	39.6	46.2	43.0	0.008

SPT: skin prick test

Table E3. Prevalence (%) of asthma and rhinitis at 19 years, by age at onset of allergic sensitization to pollen and animal, respectively.

Condition	Allergen	Age at onset of sensitization				p-value
		Never n=843	12-19 years n=184	8-12 years n=160	≤ 8 years n=323	
Current wheeze	Pollen	10.6	19.4	23.2	28.6	<0.001
	Animal	10.6	12.3	23.7	31.0	<0.001
Physician diagnosis of asthma	Pollen	10.3	17.2	25.8	33.3	<0.001
	Animal	9.2	14.1	22.9	38.1	<0.001
Current asthma	Pollen	6.2	15.6	19.4	23.4	<0.001
	Animal	6.0	9.2	16.1	28.6	<0.001
Current symptoms of rhinitis	Pollen	15.3	36.1	54.2	65.6	<0.001
	Animal	15.0	48.5	55.9	53.2	<0.001
Physician diagnosis of rhinitis	Pollen	2.9	10.0	45.2	58.3	<0.001
	Animal	3.4	26.4	34.7	44.0	<0.001
Current rhinitis	Pollen	2.5	9.4	40.0	50.5	<0.001
	Animal	2.9	22.7	32.2	38.5	<0.001
Current wheeze or symptoms of rhinitis	Pollen	22.3	42.8	59.4	71.4	<0.001
	Animal	21.6	51.5	63.6	61.5	<0.001
Current asthma or rhinitis	Pollen	7.9	21.1	47.7	58.3	<0.001
	Animal	7.9	27.6	39.8	52.4	<0.001

Table E4. Risk for asthma and rhinitis at 19 years among women, by age at onset of allergic sensitization to any allergen, pollen and animal, respectively. Analyzed by Poisson regression analyses and presented as Risk Ratios (RR) with 95% Confidence intervals (95% CI)

Type of sensitization	Age at onset of sensitization	Dependent variables among women			
		Current Wheeze	Current asthma	Current symptoms of rhinitis	Current rhinitis
Any SPT	≤ 8 years	2.80 (1.87-4.19)	3.98 (2.40-6.60)	4.27 (3.13-5.83)	25.2 (12.1-52.5)
	8-12 years	2.40 (1.41-4.10)	2.56 (1.26-5.20)	3.80 (2.57-5.63)	18.9 (8.46-42.1)
	12-19 years	1.61 (0.93-2.77)	2.06 (1.06-4.04)	2.70 (1.83-3.99)	3.84 (1.39-10.6)
	Never	1	1	1	1
Any animal	≤ 8 years	2.74 (1.84-4.10)	4.08 (2.53-6.59)	7.75 (5.14-11.7)	17.7 (9.64-32.4)
	8-12 years	2.77 (1.62-4.76)	3.19 (1.61-6.32)	9.19 (5.64-15.0)	18.0 (8.96-36.0)
	12-19 years	1.26 (0.68-2.35)	1.49 (0.69-3.23)	5.35 (3.27-8.74)	8.91 (4.36-18.2)
	Never	1	1	1	1
Any pollen	≤ 8 years	3.01 (1.96-4.61)	3.06 (1.80-5.22)	8.14 (5.41-12.2)	20.8 (11.7-37.0)
	8-12 years	2.03 (1.19-3.48)	2.14 (1.09-4.19)	6.55 (4.16-10.3)	14.3 (7.68-26.8)
	12-19 years	1.70 (1.02-2.81)	2.39 (1.36-4.20)	3.88 (2.41-6.26)	3.51 (1.57-7.82)
	Never	1	1	1	1

Adjusted for sex, family history of condition (asthma or allergic rhinitis, respectively), rural/urban living, any furry animal at home, and having a smoking mother at age 8.

SPT: skin prick test

Table E5. Risk for asthma and rhinitis at 19 years among men, by age at onset of allergic sensitization to any allergen, pollen and animal, respectively. Analyzed by Poisson regression analyses and presented as Risk Ratios (RR) with 95% Confidence intervals (95%CI).

Type of sensitization	Age at onset of sensitization	Dependent variables			
		Current Wheeze	Current asthma	Current symptoms of rhinitis	Current rhinitis
Any SPT	≤ 8 years	2.84 (1.73-4.68)	6.21 (3.20-12.0)	5.18 (3.41-7.86)	19.9 (9.50-41.5)
	8-12 years	2.36 (1.27-4.37)	4.14 (1.85-9.25)	4.84 (3.01-7.78)	13.9 (6.30-30.6)
	12-19 years	1.38 (0.65-2.94)	2.91 (1.18-7.16)	2.79 (1.60-4.86)	3.87 (1.40-10.7)
	Never	1	1	1	1
Any animal	≤ 8 years	3.18 (1.98-5.09)	5.10 (2.92-8.90)	9.82 (5.60-17.2)	8.82 (5.20-15.0)
	8-12 years	1.49 (0.71-3.10)	1.75 (0.70-4.38)	8.93 (4.76-16.7)	6.02 (3.19-11.4)
	12-19 years	1.17 (0.54-2.51)	1.54 (0.62-3.83)	8.96 (4.91-16.4)	5.95 (3.26-10.9)
	Never	1	1	1	1
Any pollen	≤ 8 years	2.32 (1.35-4.00)	4.26 (2.27-7.96)	14.4 (8.07-25.8)	20.3 (10.5-39.1)
	8-12 years	2.44 (1.37-4.34)	4.74 (2.46-9.16)	11.6 (6.30-21.3)	17.5 (8.94-34.3)
	12-19 years	2.00 (1.08-3.67)	2.58 (1.19-5.60)	5.01 (2.44-10.2)	3.70 (1.48-9.22)
	Never	1	1	1	1

Adjusted for sex, family history of condition (asthma or allergic rhinitis, respectively), rural/urban living, any furry animal at home, and having a smoking mother at age 8.

SPT: skin prick test

Fig 1.

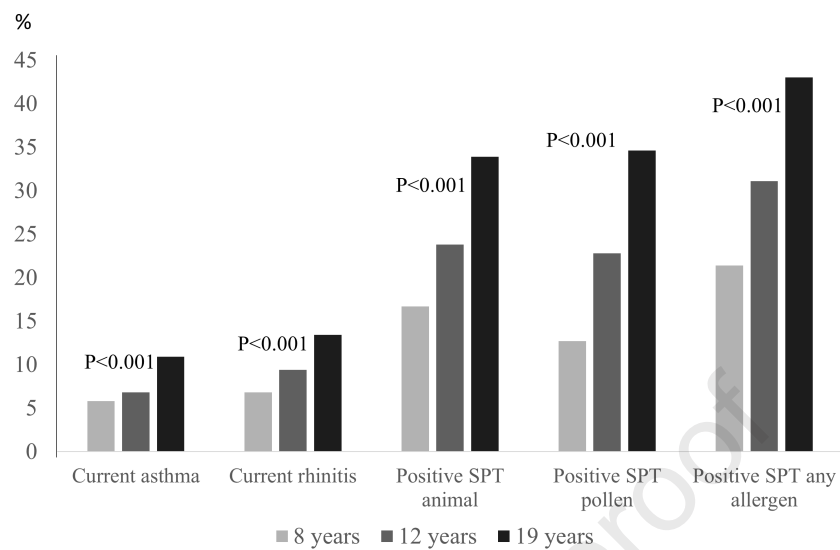


Fig. 2

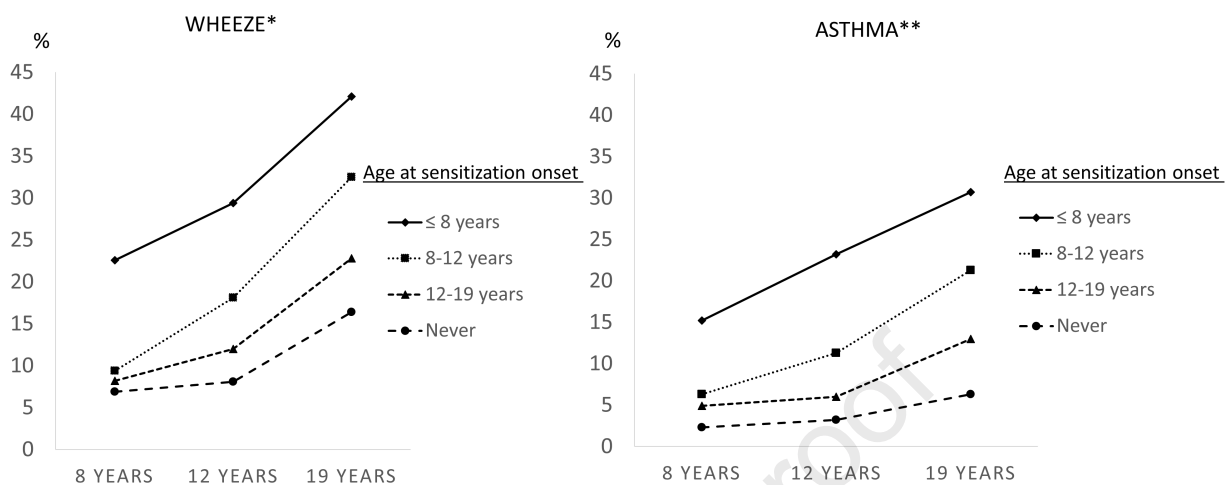


Fig. 3

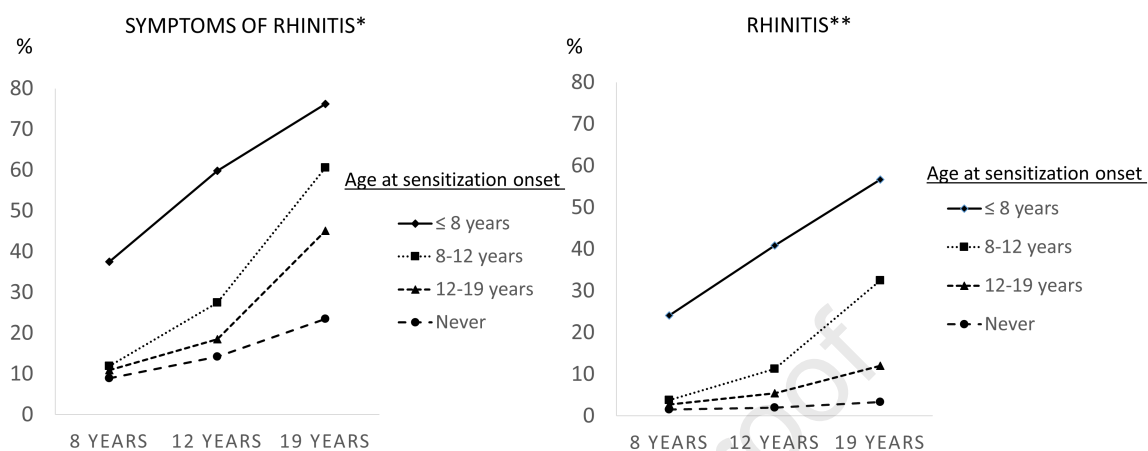


Fig. 4

