

The Majority of Children Sensitized Before School-Age Develop Allergic Disease Before Adulthood: A Longitudinal Population-Based Study



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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 is warranted in children sensitized before school-age, because they rarely remain asymptomatic until adolescence, and early diagnosis of allergy is essential for interventions and treatment.

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 1 and 2 (median age, 8 years) in 2 municipalities in Northern Sweden were invited to undergo skin prick tests and answer a questionnaire about allergic diseases, and 88% participated. At ages 12 and 19 years, the protocol was repeated, and 1510 individuals participated in all 3 examinations. Specific IgE data were collected in a random sample at age 19 years ($n = 770$). Onset of sensitization was defined: 8 years or less, 8 to 12

years, 12 to 19 years, and never sensitized. Adjusted Poisson regression was used to calculate risk ratios (RRs).

RESULTS: At 19 years, those sensitized at 8 years of age or earlier had the highest risk of asthma (RR, 4.68; 95% CI, 3.15-6.97) and rhinitis (RR, 22.3; 95% CI, 13.3-37.6), and 84% had developed either asthma or rhinitis. The combination of sensitization at age 8 years or earlier and family history of allergic diseases rendered high risks for asthma (RR, 10.6; 95% CI, 6.71-16.7) and rhinitis (RR, 36.3; 95% CI, 18.9-69.7). Individuals sensitized at age 8 years or earlier showed significantly highest level of sensitization, as judged by number of positive skin test results and titers of specific IgE.

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Abbreviations used

RR- risk ratio

SPT- skin prick test

CONCLUSIONS: Most individuals with sensitization at age 8 years or earlier developed asthma or rhinitis before young adulthood. The high level of sensitization in those sensitized early contributes to the high incidence of allergic airway conditions. © 2021 The Authors. Published by Elsevier Inc. on behalf of the American Academy of Allergy, Asthma & Immunology. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>). (J Allergy Clin Immunol Pract 2022;10:577-85)

Key words: Allergic sensitization; Asthma; Rhinitis; Longitudinal study; Cohort study

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 although 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 Although 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 age 19 years.

METHODS**Study population**

In 1996, within the research program Obstructive Lung Disease 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, aged 7 to 8 years (median, 8 years), in 3 municipalities of Northern Sweden were invited to participate in the study. From first grade, school is mandatory in Sweden. All children in 2 of the municipalities were also invited to skin prick test (SPT) for common airborne allergens.^{22,23} The cohort was reexamined at 11 to 12 years (median, 12 years) and 19 years.^{11,20,26,27} At recruitment, participation in the questionnaire was 97%, and 88% (n = 2148) participated in SPT. This article is based on the 1510 individuals (70% of the participants at age 8 years) who participated in SPT at all 3 examinations. At age 19 years, at the same occasion as the SPT, 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, and symptoms and risk factors for allergic sensitization, asthma, and allergic rhinitis.^{22,29} The questions regarding symptoms and diseases were identical in the 3 surveys. The first 2 questionnaires were distributed by the schools and completed by the caregivers, predominantly mothers, whereas 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 recommendations.³¹ The test panel included 10 common airborne allergens: birch, timothy, mugwort, dog, cat, horse, *Dermatophagoides farinae*, *Dermatophagoides 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 or more 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, Uppsala, Sweden.¹¹ The detection level for serum IgE was 0.35 International Unit/mL, and levels below that were set to 0.18 International Unit/mL.

Definitions

The main definitions are presented below, and a complete list of definitions is presented in [Table E1](#) in this article's Online Repository at www.jaci-inpractice.org.

The definition of age at onset of sensitization was based on the 3 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 result was at age 8 years; that is, development of sensitization occurred at age 8 years or earlier.

8-12 years: First time of reading a positive SPT result was at age 12 years; that is, development of sensitization occurred between age 8 and 12 years.

12-19 years: First time of reading a positive SPT result was at age 19 years; that is, development of sensitization occurred between age 12 and 19 years.

Never: Negative SPT result 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, New York, NY). Differences in proportions between 2 groups were analyzed by χ^2 test, and by Mantel-Haentzel tests for more than 2 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 result, were analyzed by Kruskal-Wallis nonparametric test. Significance was defined as a *P* value of less than .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 (RRs) 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 *versus* rural living at age 8 years, having a smoking mother at age 8 years, ever having pets at home at age 8 years, 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, 8 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 among girls at early ages, but at age 19 years, an opposite pattern or no difference by sex was found ([Figure 1](#); see

[Table E2](#) in this article's Online Repository at www.jaci-inpractice.org).

The prevalence of *any positive SPT* result increased by age, from 21.4% at age 8 years to 31.1% (at age 12 years) and 43.0% (at age 19 years), and was significantly more common among boys than among 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 result to mite and mold was found at all ages, 1.1% to 1.5% at age 8 years, and 2.4% to 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 or earlier, 160 (11%) between age 8 and 12 years, and 184 (12%) between age 12 and 19 years, whereas 843 (56%) were never sensitized.

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

At age 19 years, the prevalence of all outcomes was highest among those sensitized at age 8 years or earlier, declined by increasing age at onset of sensitization, and was lowest among those 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 I](#); see [Table E3](#) in this article's Online Repository at www.jaci-inpractice.org).

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 with outcomes of asthma. The RR for *current rhinitis* at age 19 years was 22.3 (95% CI, 13.3-37.6) for those sensitized at age 8 years or earlier versus those never sensitized to any allergen. The corresponding RR for *current asthma* was 4.68 (95% CI, 3.15-6.97) ([Table II](#)). The pattern was similar among girls and boys (see [Tables E4](#) and [E5](#) in this article's Online Repository at www.jaci-inpractice.org).

Sensitization at age 8 years or earlier 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 those sensitized at age 8 years or earlier versus those never sensitized to any pollen, and was 12.1 (95% CI, 8.15-18.0) for those sensitized at age 8 years or earlier versus those 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 those sensitized at age 8 years or earlier vs those never sensitized to any pollen and any animal, respectively; [Table II](#)). The pattern was similar among girls and boys ([Tables 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 at age 8 years or earlier compared with 16.4% among those 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 years was 76.2% among those sensitized at age 8 years or earlier versus 23.5% among those never sensitized. The corresponding figures for *current rhinitis* were 56.7% among those sensitized at age 8 years or earlier versus 3.3% among those never sensitized ([Figure 3](#)). At age 19 years, 84.2% of those sensitized at age 8 years or earlier had reported symptoms or

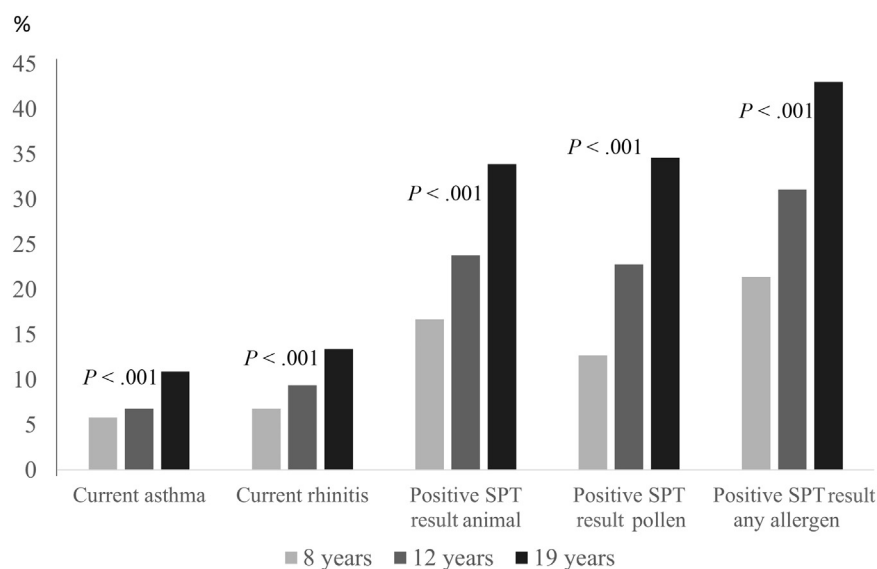


FIGURE 1. Prevalence (%) of asthma, rhinitis, and allergic sensitization (positive skin prick test result) by increasing age at examination.

TABLE I. Prevalence (%) of asthma and rhinitis at 19 y, 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, <i>P</i> value
	Never (n = 843)	12-19 y (n = 184)	8-12 y (n = 160)	≤8 y (n = 323)	
Current wheeze					
Girls	11.7	18.6	29.4	33.1	<.001
Boys	7.3	10.3	18.5	21.9	<.001
All	9.6	14.7	23.1	26.9	<.001
Physician diagnosis of asthma					
Girls	9.7	15.5	19.1	32.4	<.001
Boys	6.8	14.9	20.7	33.7	<.001
All	8.3	15.2	20.0	33.1	<.001
Current asthma					
Girls	6.3	13.4	17.6	26.9	<.001
Boys	3.3	9.2	14.1	21.9	<.001
All	4.9	11.4	15.6	24.1	<.001
Current symptoms of rhinitis					
Girls	16.0	43.3	61.8	69.0	<.001
Boys	8.3	24.1	41.3	45.5	<.001
All	12.3	34.2	50.0	56.0	<.001
Physician diagnosis of rhinitis					
Girls	1.8	8.2	36.8	48.3	<.001
Boys	2.0	8.0	29.3	43.3	<.001
All	1.9	8.2	32.5	45.5	<.001
Current rhinitis					
Girls	1.6	8.2	33.8	44.8	<.001
Boys	1.5	8.0	23.9	36.0	<.001
All	1.5	8.2	28.1	39.9	<.001

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 that of a family history of the disease. Sensitized at age 8 years or earlier 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). The corresponding RR for *current asthma* was 10.6 (95% CI, 6.71-16.7) (Tables III and IV).

TABLE II. Risk for asthma and rhinitis at 19 y, by age at onset of allergic sensitization to any allergen, pollen, and animal, respectively, by Poisson regression analyses and presented as RR with 95% CI

Type of sensitization	Age at onset of sensitization	Dependent variable			
		Current wheeze	Current asthma	Current symptoms of rhinitis	Current rhinitis
Any SPT	≤8 y	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 y	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 y	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 y	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 y	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 y	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 y	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 y	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 y	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 y.

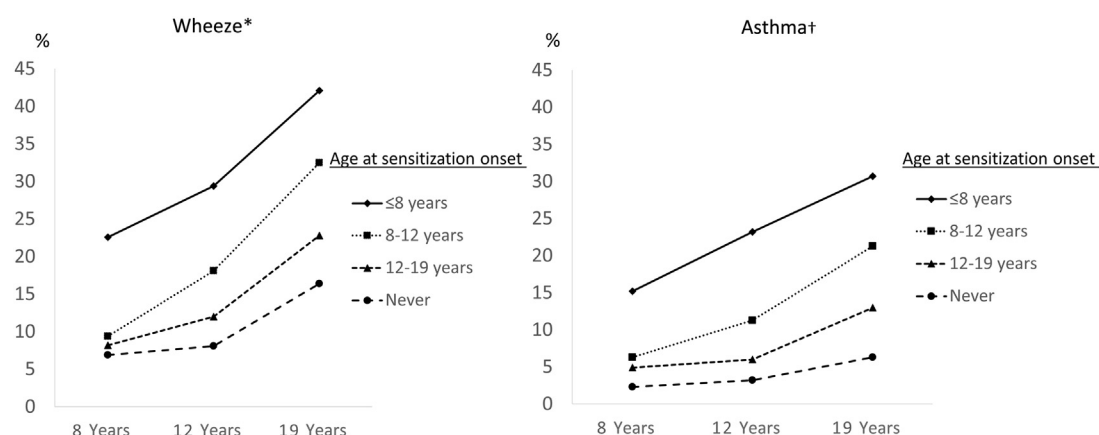


FIGURE 2. Cumulative incidence (%) of current wheeze and current asthma, respectively, by increasing age and by age at onset of allergic sensitization. *Current wheeze: "Has your child/Have you had wheezing or whistling in the chest in the last 12 months?" †Current asthma: Physician-diagnosed asthma and either current wheeze or use of asthma medication in the last 12 months.

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

At age 19 years, 66% of individuals who developed their sensitization at age 8 years or earlier had 4 or more positive SPT reactions, compared with 9.2% among those sensitized between age 12 and 19 years ($P < .001$) (Figure 4, A). Also, at first time of reading a positive SPT result, multisensitization was more common among those sensitized at age 8 years or earlier than among those who had developed sensitization later (Figure 4, B). At age 19 years, the cumulative titer of IgE antibodies to the 5 allergens analyzed (cat, dog, horse, birch, and timothy) was significantly higher among those sensitized early (geometric mean, 30.0) compared with those sensitized between age 12 and 19 years (3.21). The same pattern was found for each of the individual allergens (Table V).

DISCUSSION

In this population-based study following a cohort of children from age 8 to 19 years, 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 years, independent of sex and family history of allergic disease. In addition, children with early sensitization had higher levels of specific IgE to aeroallergens at age 19 years and were more often sensitized to multiple allergens compared with children first found to be sensitized at the preteenage or teenage stage. Finally, most children sensitized before age 8 years had experienced symptoms of asthma or rhinitis by age 19 years.

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 the time at risk when being sensitized, the higher the risk of developing clinical symptoms.^{11,19} Concordantly, at age 19 years (study end point), those who were sensitized early had higher specific IgE levels and were

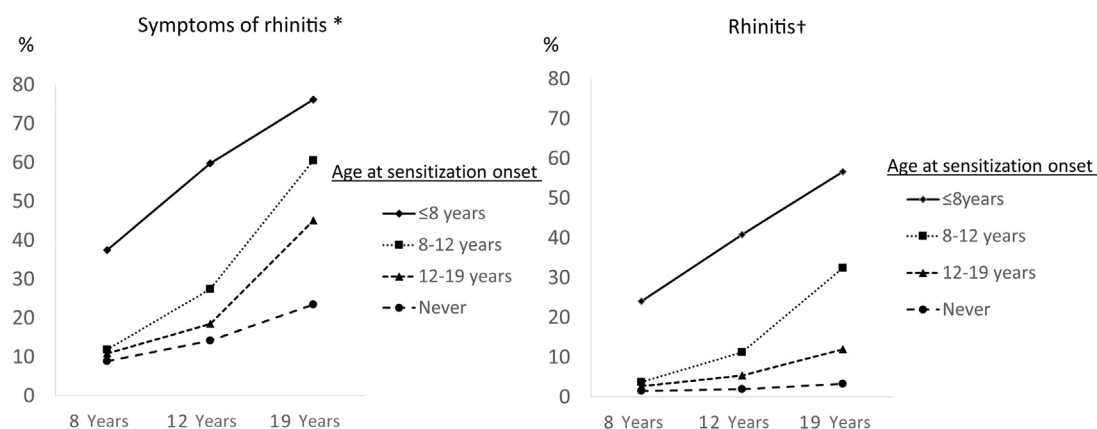


FIGURE 3. Cumulative incidence (%) of current symptoms of rhinitis and current rhinitis, respectively, by increasing age and by age at onset of allergic sensitization. *Current symptoms of rhinitis: "In the last 12 months, has your child/have you had a problem with sneezing, or a runny, or a blocked 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.

TABLE III. Cumulative incidence (%) of asthma at 19 y by age at onset of allergic sensitization to any allergen and family history

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 y	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 y	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 y	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)

Risk ratio with 95% confidence interval analyzed by Poisson regression analyses.

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

TABLE IV. Cumulative incidence (%) of rhinitis at 19 y by age at onset of allergic sensitization to any allergen and family history

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 y	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 y	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 y	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)

Risk ratio with 95% confidence interval analyzed by Poisson regression analyses.

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

more often multisensitized than those who developed sensitization later.

Notably, as presented in Figure 4, B, sensitization to multiple allergens also at first time of reading a positive SPT result was more common among those with early sensitization compared with individuals first found to be sensitized at the preteen or teenage stage. This suggests a more rapid progress of sensitization among early sensitized. Our results are in line with a British birth cohort with follow-ups up to the age of 8 years, 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 age 6 months and 13 years found that multisensitization, increasing specific IgE levels, and persistent sensitization during childhood were associated with increased risk of asthma at age 13 years.³³ Similarly, a German multicenter study showed an association between early sensitization and asthma at age 7 years.³⁴ This is in accordance with the thesis that the conditions

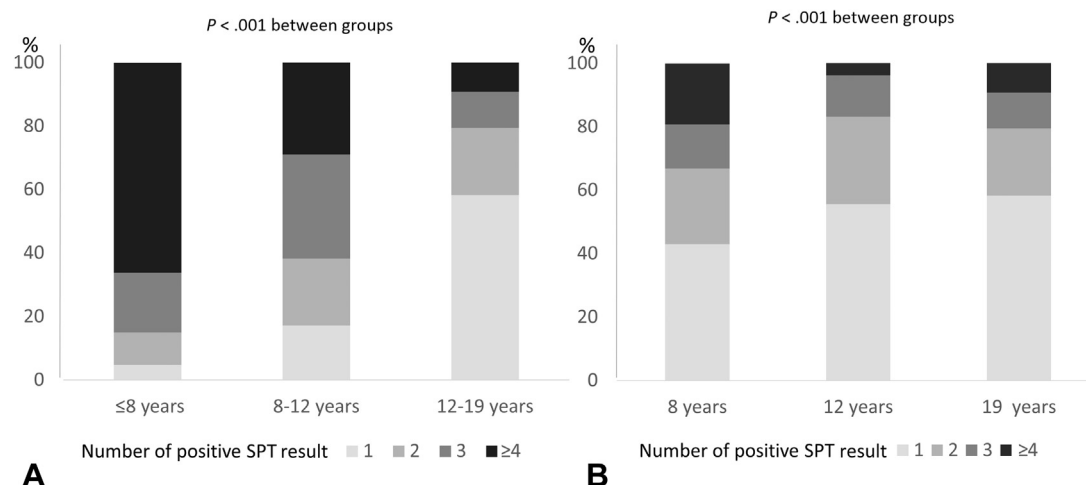


FIGURE 4. Proportion (%) of number of positive SPT results at (A) age 19 years by age at development of sensitization, and (B) at age at first reading a positive SPT result.

TABLE V. Levels of specific IgE at age 19 y expressed in geometric means and percentiles (25% and 75%) by age at onset of sensitization as measured by SPT

Sum of IgE	Age at onset of positive SPT result to any allergen			P value*
	12-19 y	8-12 y	≤8 y	
Sum of IgE†	3.21 (0.90; 12.02)	9.44 (3.40; 28.42)	30.02 (11.37; 83.85)	<.001

	Age at onset of positive SPT result to the specific allergen			P value*
	12-19 y	8-12 y	≤8 y	
Specific IgE to cat	1.44 (0.18; 7.71)	2.37 (0.18; 8.08)	4.93 (1.12; 19.2)	.001
Specific IgE to dog	0.27 (0.18; 0.18)	0.29 (0.18; 0.18)	1.10 (0.18; 3.30)	<.001
Specific IgE to horse	0.89 (0.18; 2.98)	2.02 (0.62; 8.94)	4.88 (0.63; 26.9)	.001
Specific IgE to birch	1.48 (0.41; 5.03)	4.75 (1.23; 17.2)	20.7 (8.81; 64.2)	<.001
Specific IgE to timothy	1.11 (0.18; 5.51)	4.03 (0.82; 21.4)	17.6 (7.89; 45.5)	<.001

IU, International Unit.

The lowest level of detection of IgE antibody was 0.35 IU/mL, and levels below that were given a value of 0.18 IU/mL.

*Differences by groups analyzed by Kruskal-Wallis test.

†Sum of specific IgE to cat, dog, horse, birch, and timothy.

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 such as 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 age 19 years the prevalence of these conditions was by far the highest among those sensitized early. The development of allergic

disease among those not sensitized at age 8 years was highly dependent on the development of sensitization in the subsequent years. For those who developed sensitization between age 8 and 12 years, the cumulative incidence of asthma and rhinitis at age 12 years increased considerably by the age of 19 years. For those who developed sensitization between age 12 and 19 years, the cumulative incidence of asthma and rhinitis at age 8 and 12 years was similar to the cumulative incidence in 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 3 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. Because 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, whereas 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 2 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 an RR of 4.4 for those never sensitized but with a family history compared with an RR of 31 for those sensitized early without a family history and an RR of 40 for those with both early sensitization and a family history.

Sensitization to aeroallergens was more common among boys than among girls at all 3 time points. Despite this, reported symptoms of asthma and rhinitis were more common among girls than among boys at age 19 years. Others have reported a shift in the sex distribution of asthma during adolescence, because asthma tends to be more prevalent among boys than among girls but also more prevalent among women than among men.⁴⁵⁻⁴⁷ It has also been shown that adult-onset asthma is more often nonallergic compared with 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 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 SPT 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 is in level to other studies,^{5,16,17,45} ensuring external validity. Because 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.

CONCLUSIONS

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

Allergic sensitization	
Any positive SPT result	A positive reaction (wheal diameter ≥ 3 mm) to any of the 10 tested allergens (birch, timothy, mugwort, dog, cat, horse, <i>Dermatophagoides farinae</i> , <i>Dermatophagoides 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 mo?
Physician-diagnosed asthma	Has your child/Have you been diagnosed as having asthma by a physician?
Current asthma	Physician-diagnosed asthma and either current wheeze or use of asthma medication in the last 12 mo
Current symptoms of rhinitis	In the last 12 mo, 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	Physician-diagnosed allergic rhinitis and either current symptoms of rhinitis or use of medication for rhinitis in the last 12 mo
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 y
Pets at home	Ever having had cat or dog at home as reported at age 8 y
Urban/rural living	Current living at age 8 y
Missing data	The number of missing data was very low. Missing in questions on symptoms and diseases was treated as no, whereas missing in exposures was treated as missing

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

Outcome	Age (y)	Girls (n = 755)	Boys (n = 755)	All (n = 1510)	Difference by sex,	
					P value	
Current wheeze	8	9.5	11.8	10.7	.156	
	12	6.6	8.7	7.7	.122	
	19	18.3	12.5	15.4	.002	
Physician diagnosis of asthma	8	5.0	7.7	6.4	.035	
	12	7.5	9.7	8.6	.142	
	19	15.6	15.8	15.7	.944	
Current asthma	8	4.6	6.9	5.8	.060	
	12	5.8	7.8	6.8	.126	
	19	12.2	9.7	10.9	.117	
Current symptoms of rhinitis	8	13.2	17.9	15.6	.013	
	12	17.7	21.9	19.8	.045	
	19	33.8	22.9	28.3	<.001	
Physician diagnosis of rhinitis	8	5.8	9.8	7.8	.004	
	12	9.9	14.4	12.2	.007	
	19	14.7	15.8	15.2	.567	
Current rhinitis	8	5.2	8.3	6.8	.014	
	12	7.0	11.8	9.4	.002	
	19	13.6	13.1	13.4	.762	
Any positive SPT result	8	19.2	23.6	21.4	.038	
	12	27.2	35.0	31.1	<.001	
	19	39.6	46.2	43.0	.008	

TABLE E3. Prevalence (%) of asthma and rhinitis at 19 y, 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 y (n = 184)	8-12 y (n = 160)	≤8 y (n = 323)	
Current wheeze	Pollen	10.6	19.4	23.2	28.6	<.001
	Animal	10.6	12.3	23.7	31.0	<.001
Physician diagnosis of asthma	Pollen	10.3	17.2	25.8	33.3	<.001
	Animal	9.2	14.1	22.9	38.1	<.001
Current asthma	Pollen	6.2	15.6	19.4	23.4	<.001
	Animal	6.0	9.2	16.1	28.6	<.001
Current symptoms of rhinitis	Pollen	15.3	36.1	54.2	65.6	<.001
	Animal	15.0	48.5	55.9	53.2	<.001
Physician diagnosis of rhinitis	Pollen	2.9	10.0	45.2	58.3	<.001
	Animal	3.4	26.4	34.7	44.0	<.001
Current rhinitis	Pollen	2.5	9.4	40.0	50.5	<.001
	Animal	2.9	22.7	32.2	38.5	<.001
Current wheeze or symptoms of rhinitis	Pollen	22.3	42.8	59.4	71.4	<.001
	Animal	21.6	51.5	63.6	61.5	<.001
Current asthma or rhinitis	Pollen	7.9	21.1	47.7	58.3	<.001
	Animal	7.9	27.6	39.8	52.4	<.001

TABLE E4. Risk for asthma and rhinitis at 19 y among women, by age at onset of allergic sensitization to any allergen, pollen, and animal, respectively

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 y	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 y	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 y	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 y	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 y	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 y	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 y	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 y	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 y	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

Analyzed by Poisson regression analyses and presented as RRs with 95% CI.

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 y.

TABLE E5. Risk for asthma and rhinitis at 19 y among men, by age at onset of allergic sensitization to any allergen, pollen, and animal, respectively

Type of sensitization	Age at onset of sensitization	Dependent variables			
		Current wheeze	Current asthma	Current symptoms of rhinitis	Current rhinitis
Any SPT	≤8 y	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 y	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 y	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 y	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 y	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 y	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 y	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 y	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 y	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

Analyzed by Poisson regression analyses and presented as RRs with 95% CI.

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 y.