

Allergic sensitization is age-dependently associated with rhinitis, but less so with asthma

Katja Warm, MD,^a Linnea Hedman, PhD,^b Anne Lindberg, MD, PhD,^a Jan Lötval, MD, PhD,^c Bo Lundbäck, MD, PhD,^c and Eva Rönmark, PhD^b Umeå and Gothenburg, Sweden

Background: Epidemiologic data describing the association between allergic sensitization and asthma and allergic rhinitis in adults are scarce.

Objective: To determine the prevalence and impact of specific sensitization to airborne allergens on asthma and allergic rhinitis among adults in relation to age.

Methods: A random population sample (age 21-86 years) was examined with structured interview and analysis of specific IgE to 9 common airborne allergens. Of those invited, 692 (68%) subjects participated in blood sampling. IgE level of 0.35 U/mL or more to the specific allergen was defined as a positive test result.

Results: Allergic sensitization decreased with increasing age, both in the population sample and among subjects with asthma and allergic rhinitis. In a multivariate model, sensitization to animal was significantly positively associated with asthma (odds ratio [OR], 4.80; 95% CI, 2.68-8.60), whereas sensitization to both animal (OR, 3.90; 95% CI, 2.31-6.58) and pollen (OR, 4.25; 95% CI, 2.55-7.06) was significantly associated with allergic rhinitis. The association between allergic sensitization and rhinitis was consistently strongest among the youngest age group, whereas this pattern was not found for asthma. The prevalence of allergic sensitization among patients with asthma

decreased by increasing age of asthma onset, 86% with asthma onset at age 6 y or less, 56% at age 7 to 19 years, and 26% with asthma onset at age 20 years or more.

Conclusions: Sensitization to animal was associated with asthma across all age groups; allergic rhinitis was associated with sensitization to both pollen and animal and consistently stronger among younger than among older adults. Early onset of asthma was associated with allergic sensitization among adults with asthma. (J Allergy Clin Immunol 2015;■■■:■■■-■■■.)

Key words: Adults, allergic rhinitis, allergic sensitization, asthma, epidemiology, specific IgE

The strong association between allergic sensitization and asthma and rhinitis has been well described in children, adolescents, and young adults.¹⁻³ However, data about the association of allergic sensitization with asthma, respiratory symptoms, and rhinitis in older adults are very limited.^{4,5} Because of the increasing proportion of elderly people in the general population worldwide, a better understanding of the impact of allergic sensitization on airway diseases in older ages is important.

Studies of allergic sensitization in relation to age have consistently reported an increase in prevalence from childhood to young adulthood, whereas thereafter it decreases with age.⁶⁻⁸ Normal aging partly explains the decrease in the prevalence of allergic sensitization with increasing age among adults,⁸ and a cohort effect may contribute as well.⁹ Similarly, the prevalence of allergic rhinitis is known to increase from childhood and adolescence to young adulthood, and thereafter it decreases by increasing age.^{10,11}

Both asthma and rhinitis are heterogeneous conditions and include both sensitized and nonsensitized phenotypes.¹²⁻¹⁴ Allergic sensitization is important to consider because it affects both the persistence and the severity of allergic respiratory diseases.^{15,16} A stronger impact of allergic sensitization on rhinitis than on asthma has been hypothesized.¹⁷ Furthermore, these diseases may be associated with different specific allergens. Moreover, the major airborne allergens differ by geographical area.^{18,19}

The aims of this study were to determine the prevalence and impact of allergic sensitization patterns to different airborne allergens on asthma and allergic rhinitis among adults, and to investigate the relationships by age. We therefore focused this work on the association of sensitization with asthma and rhinitis by age, including the age of onset of asthma.

METHODS

Study area

The study was performed within the Obstructive Lung Diseases in Northern Sweden Studies in Norrbotten, the northernmost county of Sweden. The county is sparsely inhabited, with approximately 250,000 inhabitants in an

From ^athe Division of Medicine, Department of Public Health and Clinical Medicine, the OLIN Unit, Umeå University, Umeå; ^bthe Department of Public Health and Clinical Medicine, Occupational and Environmental Medicine Unit, the OLIN Unit, Umeå University, Umeå; and ^cKrefting Research Centre, Institute of Medicine, University of Gothenburg, Gothenburg.

The studies were funded by the Swedish Heart-Lung Foundation, the Swedish Asthma-Allergy Foundation, the Swedish Research Council, Umeå University, Visare Norr, and Norrbotten County Council. Additional funding was provided by ThermoFisher Scientific, Uppsala, Sweden.

Disclosure of potential conflict of interest: K. Warm has received research support from the Swedish Heart-Lung Foundation. J. Lötval has consultant arrangements with Novartis, AstraZeneca, GlaxoSmithKline, Sanofi, and FlagShip ventures; is employed by the University of Gothenburg; has provided expert testimony for Bahr; has received research support from AstraZeneca; has received payment for lectures from AstraZeneca, Novartis, GlaxoSmithKline, and Abdilbrahim; has patents through FlagShip ventures; and has stock/stock options through FlagShip ventures. B. Lundbäck has received research support from AstraZeneca and GlaxoSmithKline; has received payment for lectures from AstraZeneca, GlaxoSmithKline, Novartis, and Takeda; and has participated in advisory board meetings for AstraZeneca, GlaxoSmithKline, and Novartis. E. Rönmark has received research support from the Swedish Heart-Lung Foundation, the Swedish Asthma-Allergy Foundation, the Swedish Research Council, Umeå University, Visare Norr, Norrbotten County Council, and ThermoFisher Scientific. The rest of the authors declare that they have no relevant conflicts of interest.

Received for publication January 2, 2015; revised June 1, 2015; accepted for publication June 11, 2015.

Corresponding author: Eva Rönmark, PhD, Department of Public Health and Clinical Medicine, Occupational & Environmental Medicine, Umeå University, SE-901 87 Umeå, Sweden. E-mail: eva.ronmark@nll.se.

0091-6749/\$36.00

© 2015 American Academy of Allergy, Asthma & Immunology

<http://dx.doi.org/10.1016/j.jaci.2015.06.015>

Abbreviations used

OR: Odds ratio

PAF: Population-attributable fraction

RR: Relative risk

area of 105,000 km². The climate is subarctic, with cold and long winters and mild summers. The study was approved by the Regional Ethical Review Board at Umeå University, Sweden.

Study population

The study population is presented in Fig E1 in this article's Online Repository at www.jacionline.org. In 2006, a random sample of the population of Norrbotten ($n = 7997$; age, 20-69 years) was invited to participate in a postal questionnaire study.²⁰ In addition, another randomly selected population sample aged 30 to 84 years, which had participated in a similar questionnaire study in 1996,²⁰ was invited to a follow-up ($n = 7,004$). Overall, 12,055 subjects (80% of invited) participated.

In 2008-2009, a randomly selected sample of questionnaire responders, stratified by the sex and age distribution of the population of Norrbotten, was invited to clinical examinations. Of the 1,016 invited subjects, 737 (73%) participated. At the time of examination, their mean age was 53 years (range, 21-86 years) and 50% were women. The examinations included a structured interview and blood sampling for specific and total IgE levels. The participants at the clinical examinations were representative for the entire study sample.²¹

Questionnaire

The Obstructive Lung Diseases in Northern Sweden questionnaire has been used in several national and international epidemiologic studies.^{11,22} Both the postal questionnaire and the structured interview focused on respiratory symptoms, asthma, rhinitis, chronic bronchitis, chronic obstructive pulmonary disease, comorbid conditions of airways diseases, and potential risk factors. The questionnaire has recently been validated against the Global Allergy and Asthma European Network questionnaire.²³

Allergic sensitization

Allergic sensitization was assessed by analyses of specific IgE antibodies in serum: birch, timothy, mugwort, cat, dog, horse, *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, and *Alternaria*. The serum samples were analyzed with the Immuno CAP system (ThermoFisher, Uppsala, Sweden). Of all participants, 692 subjects (94% of the participants) participated in blood sampling, of whom 51% were women. A positive result was defined as an IgE level of 0.35 IU/mL or more to the specific allergen.

Definitions

The prevalence of asthma, wheeze, and allergic rhinitis was assessed by a positive answer to the following questions at the interview:

Physician-diagnosed asthma: "Have you been diagnosed as having asthma by a physician?"

Current asthma: "Yes" to *Physician-diagnosed asthma* or "Have you ever had asthma?" and 1 of the following questions: "Have you had wheezing or whistling in your chest at any time in the last 12 months?" or "Have you had attacks of shortness of breath at any time in the last 12 months?" or "Have you used asthma medication regularly or as needed in the last 12 months?"

Current wheeze: "Have you had wheezing or whistling in your chest at any time in the last 12 months?"

Asthmatic wheeze: "Yes" to *Current wheeze* and "Have you been at all breathless when the wheezing noise was present?" and "Have you had this wheezing or whistling when you did not have a cold?"

Ever allergic rhinitis: "Have you or have you had allergic rhinitis or hay fever?"

Current allergic rhinitis: "Yes" to *Ever allergic rhinitis* and 1 of the following questions: "Have you had sneezing, runny nose, or nasal congestion without having a cold in the last 12 months?" or "Have you used medication for rhinitis in the last 12 months?"

Family history of asthma (allergic rhinitis): Mother, father, or sibling reporting ever having had asthma (allergic rhinitis). The information was derived from 2 separate questions.

Any allergen: IgE level of 0.35 IU/mL or more to any of the specific allergens.

Any animal: IgE level of 0.35 IU/mL or more to cat, dog, or horse.

Any pollen: IgE level of 0.35 IU/mL or more to birch, timothy, or mugwort.

Statistical analyses

Statistical analyses were performed by using the Statistical Package for the Social Sciences for Windows, Version 20.0. For comparisons of proportions, the χ^2 test and Fisher exact test were used when appropriate. Mantel-Haenszel's test for trend was applied for the assessment of the relationship between the prevalence of allergic sensitization and variables with more than 2 categories. Because total IgE data were not normally distributed, the Mann-Whitney *U* test was used for comparisons of distribution between groups. A *P* value of less than .05 was considered statistically significant.

The study population was divided into 3 age groups of similar width and of approximately similar size: 21 to 40 years, 41 to 60 years, and 61 to 86 years at the time of examination. Multiple logistic regression analyses were used to calculate the association between allergic sensitization and current asthma and current allergic rhinitis, and the associations were expressed as odds ratios (ORs) with 95% CI. These analyses were adjusted for age group, sex, smoking habits, and family history of asthma (allergic rhinitis). The analyses were also performed separately in the 3 age groups. Two models were applied when analyzing the association of asthma and allergic rhinitis with sensitization to specific allergens: the allergens were included one by one, and by including all allergens in the same model. Similar models were applied by using the variables sensitization to "any pollen," "any animal," and "any allergen."

The percentage of asthma and rhinitis cases in the population attributable to sensitization to *any allergen* was calculated by using the formula $PAF = P(RR - 1)/RR$, where PAF is the population-attributable fraction, RR is the relative risk, and *P* is the percentage of cases with allergic sensitization. RR was estimated by the adjusted OR.

RESULTS

Prevalence of allergic sensitization

The prevalence of sensitization to *any allergen* decreased with increasing age: 45% in the age group 21 to 40 years, 30% in the age group 41 to 60 years, and 15% in the age group 61 to 86 years ($P < .001$) (Table I). A similar trend of a decreasing prevalence by age was observed for the most common sensitizers: dog, cat, timothy, birch, and horse. Sensitization to mite was less common, and only 0.7% were sensitized to mold. No significant differences by sex were observed.

Prevalence of asthma and allergic rhinitis

The prevalence of allergic rhinitis, both current and ever reported, decreased significantly with increasing age, with the highest prevalence in the youngest age group (Table II). The prevalence of asthma, both when defined as physician-diagnosed and current asthma, and current and asthmatic wheeze did not differ significantly by age. No significant differences by sex for any of the disease entities were found.

TABLE I. Prevalence (%) of allergic sensitization defined by specific IgE level of 0.35 IU/mL or more by sex and age

Allergen	Sex		Difference by sex, <i>P</i> value	Age (y)			Difference by age, <i>P</i> value	All* (n = 692)
	Men (n = 342)	Women (n = 350)		22-40 (n = 154)	41-60 (n = 295)	61-86 (n = 243)		
Birch	12.6	10.6	.56	22.1	11.2	4.5	<.001	12.0
Timothy	13.5	10.3	.20	25.3	12.9	2.1	<.001	12.8
Mugwort	1.8	4.0	.08	5.2	3.4	0.8	.01	3.0
Any pollen	19.3	17.4	.53	35.1	19.7	6.2	<.001	19.4
Cat	14.6	10.3	.08	23.4	13.2	4.5	<.001	13.1
Dog	14.0	12.0	.42	22.7	14.9	4.5	<.001	13.6
Horse	7.6	6.0	.40	16.2	7.1	0.4	<.001	7.4
Any animal	17.5	14.6	.29	26.6	17.6	7.4	<.001	16.7
Any mite	5.8	6.0	.93	9.1	4.7	5.3	.16	6.1
Any mold†	0.9	0.6	.64	1.9	0.7	—	.08	0.7
Any allergen	29.2	26.6	.43	44.8	29.8	14.8	<.001	28.9

*Adjusted for the sex and age distribution of the population in the area.

†Fisher exact test was used.

TABLE II. Prevalence (%) of asthma, wheeze, and allergic rhinitis by sex and age

Respiratory condition	Sex			Age (y)			Difference by age, <i>P</i> value	All* (n = 737)
	Men (n = 361)	Women (n = 371)	Difference by sex, <i>P</i> value	22-40 (n = 171)	41-60 (n = 315)	61-86 (n = 251)		
Physician-diagnosed asthma	13.7	16.4	.32	17.0	14.3	14.7	.58	15.2
Current asthma	13.9	14.6	.79	15.5	14.3	13.3	.52	14.3
Current wheeze	30.9	31.1	.94	28.8	30.2	33.5	.29	30.9
Asthmatic wheeze	14.1	16.6	.34	16.5	16.9	12.7	.25	15.4
Ever allergic rhinitis (self-reported)	29.1	30.6	.67	38.6	31.7	21.5	<.001	30.2
Current allergic rhinitis	28.7	30.1	.68	37.9	32.3	20.1	<.001	29.7
Current asthma and allergic rhinitis	8.6	10.0	.52	11.3	10.5	6.4	.07	9.3

*Adjusted for the sex and age distribution of the population in the area.

Allergic sensitization in relation to asthma and allergic rhinitis

The prevalence of current asthma, and in particular current allergic rhinitis, was significantly higher in subjects sensitized to *any allergen* compared with nonsensitized subjects, 24.5% versus 10.7%, and 56.3% versus 17.6%, respectively. Similar patterns were found when comparing subjects with and without sensitization to the specific allergens (Table III). When including the variables one by one in the multivariate model, sensitization to *any allergen* and sensitization to the major specific allergens were positively associated with current asthma even after adjusting for confounders. When all specific allergens were included in the same model, sensitization to dog, OR 2.58 (95% CI, 1.01-6.57), and horse, OR 2.64 (95% CI, 1.02-6.84), remained significantly positively associated with current asthma, in contrast to sensitization to cat and the pollens. When using the variables *any animal* and *any pollen* as independent variables in the model, allergic sensitization to *any animal* remained significantly associated with current asthma, OR 4.80 (95% CI, 2.68-8.60), whereas sensitization to *any pollen* lost its significance (Table III).

Similarly to asthma, current allergic rhinitis was significantly associated with all sensitization variables when included one by one in the multivariate model. When the variables *any animal* and *any pollen* were used as independent variables in the same model, allergic rhinitis remained associated with both variables, OR 3.90 (95% CI, 2.31-6.58) and OR 4.25 (95% CI, 2.55-7.06), respectively. On including all major specific allergens in the same model, we found that the association between rhinitis and

sensitization to the pollens and cat remained significant, but sensitization to dog and horse did not (Table III).

The impact of allergic sensitization on asthma and allergic rhinitis was analyzed separately in the 3 age groups by multiple logistic regression analyses (Table IV). Sensitization to *any allergen*, *any pollen*, and *any animal*, respectively, was significantly associated with allergic rhinitis in all age groups, and the OR was considerably higher in subjects aged 20 to 40 years than in those older than 40 years. Regarding asthma, the corresponding ORs were of similar magnitude in all age groups, although not significant in those older than 60 years concerning sensitization to any allergen and to any pollen. Sensitization to *any animal* was strongly associated with asthma in all age groups.

The total IgE level was significantly higher among subjects with asthma and rhinitis, respectively, than among subjects without these conditions. This pattern was found in all age groups but reached statistical significance only for rhinitis in the 2 youngest age groups (see Table E1 in this article's Online Repository at www.jacionline.org).

Allergic sensitization among subjects with asthma and rhinitis

Among subjects with current asthma, sensitization to *any allergen* decreased significantly by age group (Table V). This pattern was also found for specific sensitization to the major allergens. In subjects with asthma aged 61 to 86 years, 22% were sensitized to at least 1 allergen compared with 68% among

TABLE III. Prevalence (%) of asthma and allergic rhinitis by sensitization status, and risk, expressed as ORs with 95% CI, of asthma and allergic rhinitis*

Allergen	Current asthma				Current allergic rhinitis			
	Prevalence	P value	OR (95% CI)†	OR (95% CI)‡	Prevalence	P value	OR (95% CI)†	OR (95% CI)‡
Timothy								
No	12.2				22.4			
Yes	31.7	<.001	3.60 (1.98-6.54)	1.54 (0.72-3.28)	72.8	<.001	7.89 (4.39-14.19)	4.31 (2.22-8.36)
Birch								
No	12.6				23.2			
Yes	29.5	<.001	3.18 (1.71-5.89)	1.07 (0.47-2.44)	69.7	<.001	6.10 (3.45-10.80)	2.59 (1.33-5.07)
Cat								
No	10.9				22.0			
Yes	40.0	<.001	6.09 (3.44-10.78)	1.61 (0.61-4.28)	73.8	<.001	8.03 (4.59-14.05)	2.49 (1.07-5.80)
Dog								
No	10.5				21.8			
Yes	41.6	<.001	6.59 (3.76-11.57)	2.58 (1.01-6.57)	72.7	<.001	7.80 (4.51-13.51)	1.88 (0.82-4.31)
Horse								
No	11.7				24.6			
Yes	54.3	<.001	9.17 (4.44-18.96)	2.64 (1.02-6.84)	82.2	<.001	10.70 (4.64-24.70)	2.14 (0.75-6.12)
Any pollen								
No	12.1				20.2			
Yes	25.2	<.001	2.65 (1.54-4.55)	1.39 (0.75-2.59)	64.8	<.001	6.45 (4.01-10.36)	4.25 (2.55-7.06)
Any animal								
No	10.4				21.0			
Yes	36.4	<.001	5.45 (3.21-9.28)	4.80 (2.68-8.60)	67.0	<.001	6.21 (3.83-10.07)	3.90 (2.31-6.58)
Any allergen								
No	10.7				17.6			
Yes	24.5	<.001	2.94 (1.81-4.77)		56.3	<.001	5.31 (3.53-7.99)	

*The analyses are based on the 692 subjects with data about allergic sensitization, of whom 100 had current asthma and 194 had current rhinitis.

†Adjusted for age, sex, smoking, and family history of asthma (allergic rhinitis). The sensitization variables (allergens) were included one by one.

‡Adjusted for age, sex, smoking, and family history of asthma (allergic rhinitis). All sensitization variables (allergens) were included in the model.

TABLE IV. Risk, expressed as ORs and 95% CI for current asthma and rhinitis, respectively, by allergic sensitization,* analyzed separately for each age group and adjusted for confounders†

Allergen	Age (y)	Current asthma			Current allergic rhinitis		
		(n‡)	OR	(95% CI)	(n§)	OR	(95% CI)
Any pollen	22-40	(25/154)	3.98	(1.43-11.14)	(54/154)	13.70	(5.47-34.31)
	41-60	(43/295)	1.98	(0.94-4.19)	(91/295)	4.40	(2.35-8.26)
	61-86	(32/243)	4.01	(0.96-16.81)	(49/243)	8.37	(2.45-28.55)
Any animal	22-40	(25/154)	3.96	(1.41-11.15)	(54/154)	16.82	(6.20-45.64)
	41-60	(43/295)	5.93	(2.84-12.39)	(91/295)	6.03	(3.08-11.82)
	61-86	(32/243)	6.78	(2.09-21.99)	(49/243)	3.45	(1.15-10.35)
Any allergen	22-40	(25/154)	3.53	(1.27-9.81)	(54/154)	19.84	(7.24-54.40)
	41-60	(43/295)	3.17	(1.59-6.31)	(91/295)	5.41	(3.07-9.54)
	61-86	(32/243)	2.07	(0.74-5.79)	(49/243)	2.39	(1.03-5.55)

*The reference group in each analysis was the group of subjects not sensitized to the respective allergen.

†Adjusted for sex, family history of asthma (allergic rhinitis), and smoking habits.

‡Number of subjects with asthma by number of all subjects in the age group.

§Number of subjects with rhinitis by number of all subjects in the age group.

subjects with asthma aged 21 to 40 years. All sensitized subjects with asthma in the oldest age group were sensitized to either cat or dog (data not included in table). Similar to the pattern in subjects with asthma, sensitization to *any allergen* as well as to specific allergens decreased significantly by increasing age among subjects with allergic rhinitis (Table V).

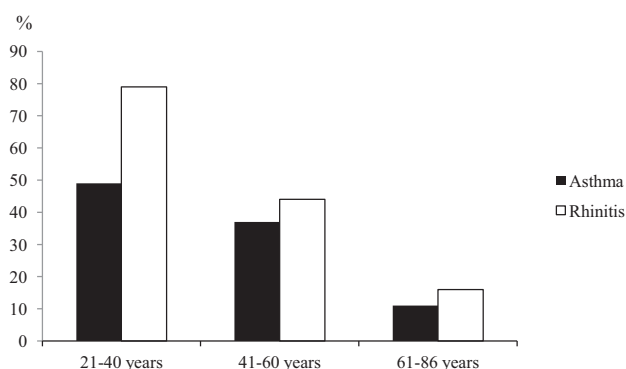
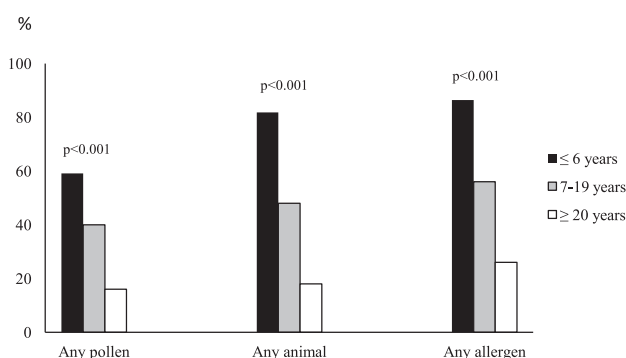
The proportion of asthma and rhinitis cases attributable to sensitization to *any allergen* was calculated separately for each age group. The PAF for asthma was 49% in the age group 21 to 40 years, 37% in the age group 41 to 60 years, and 11% in the age group 61 to 86 years. The corresponding PAFs for rhinitis

were higher, 79%, 44%, and 16% among the respective age groups (Fig 1).

Among subjects with asthma, the prevalence of allergic sensitization decreased with increasing age of asthma onset; 86% among those with asthma onset at 6 years or younger were sensitized to any allergen, 56% among those with asthma onset between 7 and 19 years, and 27% among those with asthma onset at 20 years or older (Fig 2). Because both increasing age of asthma onset and age at examination were negatively associated with allergic sensitization among subjects with asthma, both variables were included in a multiple logistic regression analysis. In this

TABLE V. Prevalence (%) of sensitization defined by IgE level of 0.35 IU/mL or more among subjects with asthma and allergic rhinitis, by age

Specific IgE	Current asthma				Current allergic rhinitis			
	22-40 y (n = 25)	41-60 y (n = 43)	61-86 y (n = 32)	Difference by age, <i>P</i> value	22-40 y (n = 54)	41-60 y (n = 91)	61-86 y (n = 94)	Difference by age, <i>P</i> value
Birch	48.0	18.6	9.4	.001	48.1	22.0	14.3	<.001
Timothy	52.0	25.6	6.2	<.001	55.6	27.5	8.2	<.001
Any pollen	60.0	30.2	12.5	<.001	70.4	36.3	20.4	<.001
Cat	52.0	37.2	15.6	.004	55.6	28.6	12.2	<.001
Dog	52.0	44.2	15.6	.004	51.9	31.9	14.3	<.001
Horse	48.0	30.2	—	<.001	40.7	16.5	—	<.001
Any animal	52.0	46.5	21.9	.02	59.3	35.2	18.4	<.001
Any mite	12.0	4.7	3.1	.18	14.8	5.5	4.1	.04
Any mold	8.0	2.3	—	.09	5.6	1.1	—	.05
Any allergen	68.0	53.5	21.9	<.001	83.3	53.8	26.5	<.001

**FIGURE 1.** The PAF% of allergic sensitization for asthma and allergic rhinitis, respectively, by age group.**FIGURE 2.** Prevalence of allergic sensitization among subjects with current asthma by age of onset of asthma.

model, allergic sensitization to *any allergen* remained negatively and significantly associated with increasing age of asthma onset, whereas age at examination did not (data not shown).

DISCUSSION

In this study of adults, a major finding includes a marked decrease in allergic sensitization among subjects with asthma with increasing age of asthma onset. Of those with asthma onset before the age of 6 years, 86% were sensitized in adulthood, whereas only 26% of the subjects with asthma with an adult onset (age ≥ 20 years) of asthma were sensitized. Furthermore, the PAF of allergic sensitization for asthma was 49% for the age group 22 to 40 years but only 11% for the age group 61 to 86 years. As expected, the corresponding figures for allergic rhinitis were higher, 79% and 16%, respectively. Moreover, we here describe distinct differences in the association between asthma and allergic rhinitis versus allergic sensitization because allergic sensitization was similarly associated with asthma regardless of age.

The prevalence of allergic sensitization and allergic rhinitis decreased considerably by increasing age, in line with previous studies,^{6,21,22,24} whereas the prevalence of asthma decreased slightly but not significantly by age. Reports of prevalence of asthma by age vary; however, most studies have found asthma to be most common among young adults.^{20,25} Over the last 5 decades, we have observed an increased prevalence of both allergy

and asthma, primarily in children. Importantly, those children have now become adults, and information on their maintained morbidity has previously been insufficiently reported.

Among both subjects with asthma and subjects with allergic rhinitis, the prevalence of sensitized subjects decreased considerably by age, among subjects with asthma from 68.0% in the age group 21 to 40 years to 21.9% in the age group 61 to 86 years, and the corresponding result for allergic rhinitis was 83.3% to 26.5%. The high prevalence of allergic sensitization in young adults was expected and indicates a high validity of the interview question on allergic rhinitis in these ages. However, among subjects older than 61 years, the low prevalence of allergic sensitization indicates a lower validity of the question. The reason for this is unclear, but we have in a previous publication reported high remission of allergic sensitization among elderly people.⁸ Thus, subjects who had allergic rhinitis at a young age may have outgrown the allergic component but the rhinitis has remained as a nonallergic rhinitis. This is in line with a long-term follow-up of adults with rhinitis.²⁶

In analyses adjusted for confounders, allergic sensitization as a risk factor for allergic rhinitis yielded a high-risk estimate in young adults aged 22 to 40 years, whereas it was clearly lower but still significant in those aged 61 years or older. This strong association is also reported by others.²² A similar pattern was found for sensitization to any pollen and any animal. Interestingly, in contrast to rhinitis, the corresponding risk estimates for

asthma were similar irrespective of age group, a result not found previously in the literature.

Furthermore, both in the univariate risk analyses and when added one by one in a multivariate model adjusting for confounders, allergic sensitization to each of the major sensitizers was significantly associated with asthma and even more strongly with allergic rhinitis. The results are similar to findings from the European Community Respiratory Health Survey²⁷ and from studies in Finland²² and Estonia,²⁴ whereas the Finnish and Estonian studies were insufficiently powered for such comparisons. Also, other studies have found stronger associations between allergic sensitization and rhinitis than with asthma.^{28,29} It is well known that asthma is also associated with several environmental factors including smoking and traffic exhausts, socioeconomic status, and obesity, whereas rhinitis has been mainly associated with allergic sensitization.^{15,27,29}

In a multivariate model including all major specific allergens, sensitization to timothy, birch, and cat remained significantly associated with allergic rhinitis, whereas sensitization to horse and dog did not become significant. On the contrary, asthma remained significantly associated with sensitization to dog and horse, whereas timothy, birch, and cat lost their significance. These results correspond well to studies conducted among children.^{12,30} Also, results from studies of adult populations point to a stronger association between sensitization to indoor allergens, such as mites and pets, and asthma compared with allergic rhinitis.³¹ The influence of perennial allergen exposure in contrast to seasonal pollen exposure might contribute to our findings. The more continuous exposure from perennial allergens might have a potentially stronger effect on lower airways in contrast to the relatively short period of exposure from pollen, especially in our study area. Furthermore, in contrast to cat allergens, which are very small and may remain in the air for a long time,³² pollens are larger and also seem to be dependent on other environmental factors to affect the lower airways.³³ In many geographical areas, house dust mite is the most important specific allergen related to asthma.³⁴ However, sensitization to mite is uncommon^{7,19} in Northern Sweden, probably due to the cold and dry climate.

The strong association between asthma and sensitization to furry animals also found among the middle-aged and elderly was somewhat surprising because we already know that sensitization fades by age. In line with our results, a high prevalence of bronchial hyperresponsiveness has been found in elderly with elevated levels of specific IgE to cat,³⁵ and a longitudinal study from the European Community Respiratory Health Survey among young and middle-aged adults reported sensitization to cat being independently associated with new-onset asthma.²⁷

Sensitization to pollen has been strongly associated with rhinitis according to most studies,^{14,36,37} but few, if any, have analyzed sensitization to pollen as a risk factor for rhinitis in different age groups, including the elderly. Importantly, in our study, the association between allergic rhinitis and sensitization remained significant in the oldest age group also, even though the risk estimates decreased in strength with increasing age. In addition to sensitization to pollen, sensitization to animal yielded ORs of a similar level. The association between sensitization to any animal and allergic rhinitis also reached significance in the age group 61 years or older. Also, other studies have reported allergens other than pollen to be associated with rhinitis.²⁹ Among subjects of similar ages as in our study, Bousquet et al¹⁴ reported

sensitization to pollen and mites to be the major allergens associated with allergic rhinitis.

Very few studies have calculated the PAF of allergic sensitization for asthma or allergic rhinitis.^{25,27} The US National Health and Nutrition Examination Survey found 56% of asthma cases to be attributable to atopy among subjects aged 20 to 59 years,²⁵ which is somewhat higher than in similar ages in our study. As expected, a higher percentage of cases of allergic rhinitis was attributable to sensitization to any allergen in our study, especially in the 2 younger age groups. However, about 10% of asthma cases and about 15% of the cases of allergic rhinitis among the elderly can be related to allergic sensitization, emphasizing that allergic sensitization also is of importance among the elderly.

In line with others,³⁸ we also found the total IgE level to be significantly associated with both asthma and rhinitis and with a similar pattern in all age groups. However, the total IgE level is more unspecific compared with the specific IgE level and is also influenced by factors that we did not have information on, such as infections and use of medications.

Because of the cross-sectional design of our study, we were not able to assess at which age subjects had become sensitized. However, among those with asthma, we could assess the relationship between age of asthma onset and allergic sensitization. Our result, showing a significant decrease in allergic sensitization with increasing age of asthma onset, is in line with a cohort of children with asthma observed from age 7 to age 19 years, where the large majority of those with persistent asthma at age 19 years were sensitized to cat or dog at age 7 years.¹⁵ Data about the relationship between age at asthma onset and allergic sensitization among adults are scarce. In an Australian study, subjects with late-onset asthma after the age of 30 years were less likely to be sensitized.³⁹ Similar to our findings, a study from the United States reported that subjects with an early age of asthma onset had a significantly higher prevalence of skin prick test positivity and a more severe asthma.⁴⁰

In epidemiologic studies, the skin prick test is commonly used for determining the presence of allergic sensitization. Instead, we used measurements of specific IgE in serum, which is likely to reduce methodological bias because skin reactivity may be difficult to evaluate in elderly. A further strength of the present study is the population-based design, reflecting the sensitization patterns and disease prevalence in a general population, and the use of validated questionnaires. Bias due to nonparticipation is likely to be limited because the participation rate was high.⁴¹ Potential recall bias might be an issue in the assessment of age of asthma onset, and a limitation is lack of information about the age of onset of rhinitis. Despite the large sample of about 700 subjects, more detailed analyses considering sensitization to the specific allergens by age were not possible due to the low prevalence of sensitization among the elderly.

In conclusion, a different sensitization pattern was found for asthma and allergic rhinitis. Sensitization to timothy, birch, and cat was significantly associated with allergic rhinitis, whereas sensitization to dog and horse was associated with asthma. In addition, the strength of association decreased by age for allergic rhinitis, whereas the association between allergic sensitization and asthma was less dependent on age. Among adults with asthma, allergic sensitization was significantly positively related to early asthma onset. As the prevalence of allergic sensitization has increased in the general population, and because the proportion of elderly is increasing, longitudinal studies focused on the

impact of early allergic sensitization on morbidity in the elderly are needed.

We thank the research team within the Obstructive Lung Disease in Northern Sweden Studies, especially Ann-Christin Jonsson and Sigr d Sundberg for the collection of the data.

Clinical implications: Allergic rhinitis is age-dependently associated with sensitization to pollen and animal, whereas asthma is associated with sensitization to animal independent of age.

REFERENCES

- Toelle BG, Xuan W, Peat JK, Marks GB. Childhood factors that predict asthma in young adulthood. *Eur Respir J* 2004;23:66-70.
- Sears MR, Greene JM, Willan AR, Wiecek EM, Taylor DR, Flannery EM, et al. A longitudinal, population-based, cohort study of childhood asthma followed to adulthood. *N Engl J Med* 2003;349:1414-22.
- Bjerg-Backlund A, Perzanowski MS, Platts-Mills T, Sandstrom T, Lundback B, Ronmark E. Asthma during the primary school ages—prevalence, remission and the impact of allergic sensitization. *Allergy* 2006;61:549-55.
- Schofer Y, Schafer T, Meisinger C, Wichmann HE, Heinrich J. KORA Study Group. Predictivity of allergic sensitization (RAST) for the onset of allergic diseases in adults. *Allergy* 2008;63:81-6.
- Bodtger U, Poulsen LK, Linneberg A. Rhinitis symptoms and IgE sensitization as risk factors for development of later allergic rhinitis in adults. *Allergy* 2006;61:712-6.
- Linneberg A, Gislum M, Johansen N, Husemoen LL, Jorgensen T. Temporal trends of aeroallergen sensitization over twenty-five years. *Clin Exp Allergy* 2007;37:1137-42.
- Ronmark E, Bjerg A, Perzanowski M, Platts-Mills T, Lundback B. Major increase in allergic sensitization in schoolchildren from 1996 to 2006 in northern Sweden. *J Allergy Clin Immunol* 2009;124:357-63, 63.e1-15.
- Warm K, Backman H, Lindberg A, Lundback B, Ronmark E. Low incidence and high remission of allergic sensitization among adults. *J Allergy Clin Immunol* 2012;129:136-42.
- Broadfield E, McKeever TM, Scrivener S, Venn A, Lewis SA, Britton J. Increase in the prevalence of allergen skin sensitization in successive birth cohorts. *J Allergy Clin Immunol* 2002;109:969-74.
- Blomme K, Tomassen P, Lapeere H, Huvenne W, Bonny M, Acke F, et al. Prevalence of allergic sensitization versus allergic rhinitis symptoms in an unselected population. *Int Arch Allergy Immunol* 2013;160:200-7.
- Eriksson J, Ekerljung L, Pullerits T, Holmberg K, Ronmark E, Lotvall J, et al. Prevalence of chronic nasal symptoms in West Sweden: risk factors and relation to self-reported allergic rhinitis and lower respiratory symptoms. *Int Arch Allergy Immunol* 2011;154:155-63.
- Ronmark E, Perzanowski M, Platts-Mills T, Lundback B. Different sensitization profile for asthma, rhinitis, and eczema among 7-8-year-old children: report from the Obstructive Lung Disease in Northern Sweden studies. *Pediatr Allergy Immunol* 2003;14:91-9.
- Westman M, Stjerne P, Asarnej A, Kull I, van Hage M, Wickman M, et al. Natural course and comorbidities of allergic and nonallergic rhinitis in children. *J Allergy Clin Immunol* 2012;129:403-8.
- Bousquet J, Annesi-Maesano I, Carat F, Leger D, Rugina M, Pribil C, et al. Characteristics of intermittent and persistent allergic rhinitis: DREAMS study group. *Clin Exp Allergy* 2005;35:728-32.
- Andersson M, Hedman L, Bjerg A, Forsberg B, Lundback B, Ronmark E. Remission and persistence of asthma followed from 7 to 19 years of age. *Pediatrics* 2013;132:e435-42.
- Zureik M, Neukirch C, Leynaert B, Liard R, Bousquet J, Neukirch F, et al. Sensitization to airborne moulds and severity of asthma: cross sectional study from European Community respiratory health survey. *BMJ* 2002;325:411-4.
- Gehring U, Heinrich J, Jacob B, Richter K, Fahlbusch B, Schlenvoigt G, et al. Respiratory symptoms in relation to indoor exposure to mite and cat allergens and endotoxins. Indoor Factors and Genetics in Asthma (INGA) Study Group. *Eur Respir J* 2001;18:555-63.
- Burbach GJ, Heinzerling LM, Edenharter G, Bachert C, Bindslev-Jensen C, Bonini S, et al. GA(2)LEN skin test study II: clinical relevance of inhalant allergen sensitizations in Europe. *Allergy* 2009;64:1507-15.
- Perzanowski MS, Ronmark E, Nold B, Lundback B, Platts-Mills TA. Relevance of allergens from cats and dogs to asthma in the northernmost province of Sweden: schools as a major site of exposure. *J Allergy Clin Immunol* 1999;103:1018-24.
- Backman H, Hedman L, Jansson SA, Lindberg A, Lundback B, Ronmark E. Prevalence trends in respiratory symptoms and asthma in relation to smoking—two cross-sectional studies ten years apart among adults in northern Sweden. *World Allergy Organ J* 2014;7:1.
- Warm K, Lindberg A, Lundback B, Ronmark E. Increase in sensitization to common airborne allergens among adults—two population-based studies 15 years apart. *Allergy Asthma Clin Immunol* 2013;9:20.
- Pallasaho P, Ronmark E, Haahtela T, Sovijarvi AR, Lundback B. Degree and clinical relevance of sensitization to common allergens among adults: a population study in Helsinki, Finland. *Clin Exp Allergy* 2006;36:503-9.
- Ekerljung L, Ronmark E, Lotvall J, Wennergren G, Toren K, Lundback B. Questionnaire layout and wording influence prevalence and risk estimates of respiratory symptoms in a population cohort. *Clin Respir J* 2013;7:53-63.
- Raukas-Kivioja A, Raukas ES, Meren M, Loit HM, Ronmark E, Lundback B. Allergic sensitization to common airborne allergens among adults in Estonia. *Int Arch Allergy Immunol* 2007;142:247-54.
- Arbes SJ Jr, Gergen PJ, Vaughn B, Zeldin DC. Asthma cases attributable to atopy: results from the Third National Health and Nutrition Examination Survey. *J Allergy Clin Immunol* 2007;120:1139-45.
- Simola M, Holopainen E, Malmberg H. Changes in skin and nasal sensitivity to allergens and the course of rhinitis: a long-term follow-up study. *Ann Allergy Asthma Immunol* 1999;82:152-6.
- Anto JM, Sunyer J, Basagana X, Garcia-Esteban R, Cerveri I, de Marco R, et al. Risk factors of new-onset asthma in adults: a population-based international cohort study. *Allergy* 2010;65:1021-30.
- L m HT, Ekerljung L, Bjerg A, V n T, Tng N, Lundb ck B, et al. Sensitization to airborne allergens among adults and its impact on allergic symptoms: a population survey in northern Vietnam. *Clin Transl Allergy* 2014;4:6.
- Plaschke PP, Janson C, Norrman E, Bj rnsson E, Ellbj r S, Jarvholm B. Onset and remission of allergic rhinitis and asthma and the relationship with atopic sensitization and smoking. *Am J Respir Crit Care Med* 2000;162:920-4.
- Stoltz DJ, Jackson DJ, Evans MD, Gangnon RE, Tisler CJ, Gern JE, et al. Specific patterns of allergic sensitization in early childhood and asthma & rhinitis risk. *Clin Exp Allergy* 2013;43:233-41.
- Shaaban R, Zureik M, Soussan D, Anto JM, Heinrich J, Janson C, et al. Allergic rhinitis and onset of bronchial hyperresponsiveness: a population-based study. *Am J Respir Crit Care Med* 2007;176:659-66.
- Luczynska CM, Li Y, Chapman MD, Platts-Mills TAE. Airborne concentrations and particle size distribution of allergen derived from domestic cats (*Felis domesticus*): measurements using cascade impactor, liquid impinge and a two-site monoclonal antibody assay for Fel d 1. *Am Rev Respir Dis* 1990;141:361-7.
- Badorrek P, Dick M, Emmert L, Schaumann F, Koch W, Hecker H, et al. Pollen starch granules in bronchial inflammation. *Ann Allergy Asthma Immunol* 2012;109:208-14.e6.
- Sunyer J, Jarvis D, Pekkanen J, Chinn S, Janson C, Leynaert B, et al. Geographic variations in the effect of atopy on asthma in the European Community Respiratory Health Study. *J Allergy Clin Immunol* 2004;114:1033-9.
- Kerkhof M, Postma DS, Schouten JP, de Monchy JG. Allergic sensitization to indoor and outdoor allergens and relevance to bronchial hyperresponsiveness in younger and older subjects. *Allergy* 2003;58:1261-7.
- Haahtela T, Burbach GJ, Bachert C, Bindslev-Jensen C, Bonini S, Bousquet J, et al. Clinical relevance is associated with allergen-specific wheal size in skin prick testing. *Clin Exp Allergy* 2014;44:407-16.
- Bauchau V, Durham SR. Epidemiological characterization of the intermittent and persistent types of allergic rhinitis. *Allergy* 2005;60:350-3.
- Salo PM, Calatroni A, Gergen PJ, Hoppin JA, Sever ML, Jaramillo R, et al. Allergy-related outcomes in relation to serum IgE: results from the National Health and Nutrition Examination Survey 2005-2006. *J Allergy Clin Immunol* 2011;127:1226-35.
- Craig TJ, King TS, Lemanske RF Jr, Wechsler ME, Icitovic N, Zimmerman RR Jr, et al. Aeroallergen sensitization correlates with PC(20) and exhaled nitric oxide in subjects with mild-to-moderate asthma. *J Allergy Clin Immunol* 2008;121:671-7.
- Miranda C, Busacker A, Balzar S, Trudeau J, Wenzel SE. Distinguishing severe asthma phenotypes: role of age at onset and eosinophilic inflammation. *J Allergy Clin Immunol* 2004;113:101-8.
- Ronmark EP, Ekerljung L, Lotvall J, Toren K, Ronmark E, Lundback B. Large scale questionnaire survey on respiratory health in Sweden: effects of late- and non-response. *Respir Med* 2009;103:1807-15.

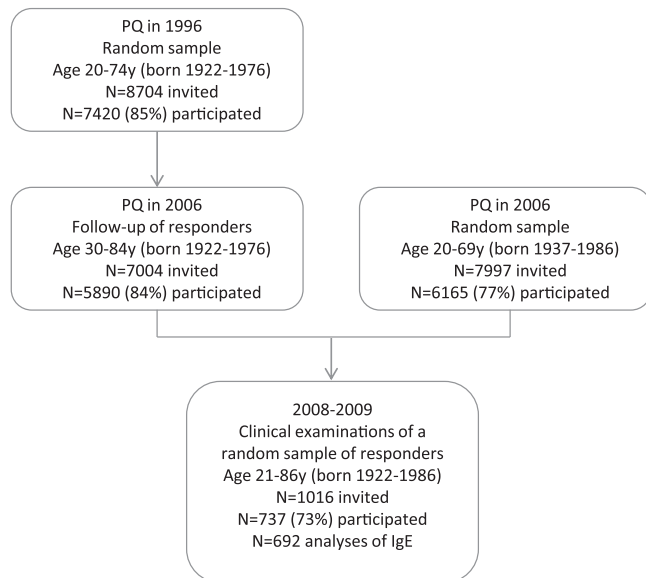


FIG E1. Flow chart of the study population. *PQ*, Postal Questionnaire Survey.

TABLE E1. Level of total IgE in relation to asthma and rhinitis by age groups

Subjects by age group and presence of asthma and allergic rhinitis	Mean	Median	Difference, <i>P</i> value*
All subjects			
Current asthma			
Yes	146.1	39.8	.005
No	72.8	27.2	
Age 21-40 y			
Current asthma			
Yes	279.5	72.3	.100
No	70.0	27.6	
Age 41-60 y			
Current asthma			
Yes	100.5	35.1	.131
No	80.1	29.7	
Age 61-86 y			
Current asthma			
Yes	107.4	40.1	.075
No	65.9	25.4	
All subjects			
Current rhinitis			
Yes	120.1	45.1	<.001
No	68.6	22.7	
Age 21-40 y			
Current rhinitis			
Yes	214.7	72.3	<.001
No	45.2	20.7	
Age 41-60 y			
Current rhinitis			
Yes	82.0	36.1	.003
No	82.1	24.5	
Age 61-86 y			
Current rhinitis			
Yes	89.0	31.7	.287
No	66.6	22.8	

*The Mann-Whitney *U* test was used for comparisons of distribution between groups (subjects with and without asthma and rhinitis, respectively).