

Increase in the prevalence of allergen skin sensitization in successive birth cohorts

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Asthma, rhinitis,
other respiratory
diseases

Background: Little is known about longitudinal trends in the prevalence of allergen skin sensitization in the general population.

Objective: We sought to measure the change in prevalence of allergen skin sensitization over a 9-year period in a cohort of adults and hence to determine whether cross-sectional differences in prevalence between age groups are due to an aging or cohort effect.

Methods: In 1991 and 2000, we measured skin sensitization, defined as a wheal diameter of 3 mm or larger than that elicited by a saline control, to *Dermatophagoides pteronyssinus*, cat fur, mixed grass, *Aspergillus fumigatus*, and *Cladosporium herbarum* in a cohort of 1339 adults from Nottingham aged between 18 and 71 years in 1991. Subjects were divided into six 9-year successive birth cohorts, and the effects of birth cohort and the within-subject change from 1991 to 2000 were analyzed in a generalized estimating equation logit model.

Results: The unadjusted prevalence of sensitization to any allergen was 30.5% in 1991 and 31.8% in 2000. In cross-sectional analyses the prevalence of sensitization decreased with increasing age at both surveys (risk ratio, 2.15; 95% confidence interval [CI], 1.45-3.17 for 18- to 26-year-old patients relative to 63- to 70-year-old patients in the 1991 survey). In longitudinal analysis there was no within-subject change in sensitization from 1991 to 2000 (adjusted odds ratio, 1.07; 95% CI, 0.97-1.19), but there was a significant cohort effect (adjusted odds ratio per successive 9 year cohort, 1.27; 95% CI, 1.18-1.37).

Conclusion: The cross-sectional decrease in allergen sensitization with age in the general population arises predominantly from a secular increase in sensitization prevalence with successive birth cohorts and not to a loss of sensitization within subjects over time. As a result of this cohort effect, the prevalence of allergic sensitization has increased in this general adult population sample. (J Allergy Clin Immunol 2002;109:969-74.)

Key words: Allergen skin sensitization, longitudinal, age, cohort effect

Abbreviations used

CI: Confidence interval

RR: Risk ratio

Allergen skin sensitization is widely used as a marker of allergy in clinical practice and epidemiologic studies, and the cross-sectional relationships between sensitization and age,¹⁻⁶ sex,^{2-4,6,7} clinical disease,^{2,8,9} other measures of allergy (eg, IgE),^{2,5,10,11} eosinophilia,^{9,11} and environmental exposures (eg, smoking)^{2,6,12-16} are well documented. To date, however, there has been relatively little research into longitudinal trends in the prevalence of allergen skin sensitization in populations^{12,13} or the effect of aging on allergen sensitization within subjects.

In cross-sectional studies allergen skin sensitization has been shown consistently to decrease with increasing age,^{1,2,4-6,9,17-20} but it is not clear whether this is due to a reduction in allergy within subjects as they grow older, a cohort phenomenon arising from a secular trend of increasing prevalence of allergy in more recent birth cohorts, or a higher mortality in allergic subjects. Because immune function changes significantly with age, with a reduction in both T-cell population and function,²¹⁻²³ it seems likely that aging effects within subjects are at least partly responsible. However, in a longitudinal study of 1333 subjects aged 3 years and older in Tucson, Ariz, over approximately 8 years during the 1970s, Barbee et al¹³ reported an overall increase in the prevalence of allergen skin sensitization, which suggests that any aging effect was more than offset by a secular trend of increasing prevalence.

In this study we examined the change in allergen skin sensitization over a 9-year period in a random sample of a cohort of adults to determine whether the cross-sectional relationship between age and the prevalence of sensitization is due to an aging effect or to a cohort effect.

METHODS

Between January and May 1991, 2633 adults aged 18 to 70 years selected at random from the electoral register of a Local Authority Area in Nottingham, United Kingdom, were tested for allergen skin sensitivity to *Dermatophagoides pteronyssinus*, cat fur, mixed grass pollen, *Aspergillus fumigatus*, and *Cladosporium herbarum* with histamine (1 mg/mL histamine in 50% glycerol) and saline controls (Bencard).²⁴ Sensitization was measured by placing a drop of each

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TABLE I. Demographic data of those participating in the original 1991 survey and those restudied in 2000

	Subjects in 1991 (n = 2633), n (%)	Subjects in 2000 (n = 1339), n (%)
Sex		
Male	1312 (49.8)	666 (49.7)
Female	1321 (50.2)	673 (50.3)
Age in 1991, y		
18-26	293 (11.1)	87 (6.5)
27-35	447 (17.0)	180 (13.4)
36-44	592 (22.5)	323 (24.1)
45-53	553 (21.0)	331 (24.7)
54-62	448 (17.0)	278 (20.8)
63-71	300 (11.4)	140 (10.5)
Smoking status in 1991		
Never	1306 (49.6)	676 (50.5)
Exsmoker	730 (27.7)	510 (38.1)
Current	597 (22.7)	153 (11.4)
Allergen sensitized in 1991	801 (30.4)	408 (30.5)

allergen solution on the volar aspect of the forearm and the skin caught with a 25-gauge hypodermic needle at 45° to catch and lift the skin. Wheal reactions were read after 15 minutes, taking the average of the largest measurable diameter and the diameter perpendicular to this. Participants were asked to refrain from taking antihistamine medication for at least 24 hours beforehand. Participants also completed an interviewer-administered computerized questionnaire based on the International Union Against Tuberculosis and Lung Disease (1984) questionnaire,²⁵ which provided information on respiratory symptoms, smoking history, and other social, medical, and occupational details.

In the year 2000, the same individuals were invited for repeat testing as part of a longitudinal study of dietary effects in asthma. When possible, participants were studied at the same time of year as in 1991 to minimize the seasonal effects on allergen skin sensitization. Those who did not respond or did not attend their appointments were sent 2 further invitations. The names of persistent nonresponders were checked against current telephone listings, and the individuals were contacted by means of telephone if possible. Allergen skin sensitization was measured by using the same technique as in 1991 but with allergen solutions from a different manufacturer (Allergopharma). Responses to Bencard and Allergopharma solutions were compared in an independent sample of 61 subjects with known allergen sensitivity who were tested with *D pteronyssinus*, cat fur, and mixed grass pollen by using both sets of allergen solutions on the same day. The studies were approved by Nottingham City Hospital Research Ethics Committee.

Definitions

Allergen skin sensitization was defined as a wheal reaction to allergen of at least 3 mm larger than that of the saline control. "Any" allergen skin sensitization included sensitization to any one or more of the 5 allergens tested. "Never smokers" were defined as those who had not smoked as much as one cigarette per day for at least 1 year, and "exsmokers" were defined as those who had not smoked for at least a month before the study. Social class was defined by occupation according to the Registrar General's classification,²⁶ combining the semiskilled and unskilled manual groups because of small numbers.

Statistical methods

Skin test responses to allergen solutions from the 2 different manufacturers were compared with paired *t* tests and the κ statistic. We used multiple logistic regression to assess the effects of age, sex,

smoking status, social class, and 3-month calendar period in which the measurements were made on the cross-sectional prevalence of allergen skin sensitization in 1991 and 2000. Subjects were then grouped into seven 9-year birth cohorts by age in 1991, and the longitudinal effects of age and birth cohort on the risk of allergic sensitization were analyzed simultaneously by using generalized estimating equation population-averaged logit models in STATA 7.0 (Stata Corp).

RESULTS

Of the 2633 subjects who took part in the original survey in 1991, 1346 (51%) provided measures in 2000. Of the 1287 who did not participate in the 2000 study, 188 (15%) had moved outside the Nottingham area, 139 (11%) had died or were unable to attend because of chronic ill health, 475 (37%) replied that they were no longer interested in participating, and 95 (7%) agreed to participate but did not attend. We were unable to establish contact with 398 (31%) subjects. Demographic data are detailed in Table I, and 7 subjects who did not abstain from antihistamines were excluded. Nonparticipants in 2000 tended to be younger and more likely to have been smokers in 1991, but there was no difference in the prevalence of allergen skin sensitization to any allergen in 1991 between those who did and did not participate in the 2000 study (1991 prevalence among participants, 30.5%; 1991 prevalence among nonparticipants, 30.3%). Of those who died between 1991 and 2000, 23.3% were sensitized to any allergen.

The 61 subjects who participated in the allergen solution comparison study comprised 32 (52%) males, had a mean $\pm$ SD age of 49.8 $\pm$ 11.8 years, and included 17.2% smokers and 34.5% exsmokers. The level of agreement between allergen skin sensitization reactions produced by the 2 manufacturers' solutions was high, with a κ value for *D pteronyssinus* of 0.80, a κ value for cat fur of 0.92, and a κ value for mixed grass pollen of 0.92. There was no difference between the 2 solutions in terms of the mean allergen wheal diameters for *D pteronyssinus* and mixed grass pollen, but the mean diameter for cat fur with the solution used in the 2000 study was significantly higher by 0.34 mm (95% confidence interval [CI], 0.03-0.65 mm; Table II).

The prevalence of sensitization to *D pteronyssinus* was 17.2% and 19.2% in 1991 and 2000, that to cat fur was 17.0% and 9.3%, that to mixed grasses was 18.8% and 18.6%, and that to any allergen was 30.5% and 31.8%, respectively. Very few subjects were sensitized to *A fumigatus* (1991, 1.4%; 2000, 3.2%) or *C herbarum* (1991, 0.4%; 2000, 2.2%), and we have not analyzed these individual responses further. In both 1991 and 2000, there was a significant cross-sectional trend of decreasing allergen skin sensitization to each of the allergens with increasing age ($P < .001$), with a prevalence of sensitization to any allergen of 46.0% in those in the youngest age group compared with 21.4% in those older than 63 years of age in 1991 (Table III). The risk ratios (RRs) and 95% CIs for allergen sensitization in 1991 relative to the oldest group (age 63-70 years) were as follows: age 18-26 years, RR of 2.15 and 95% CI of 1.45 to 3.17; age 27-35 years,

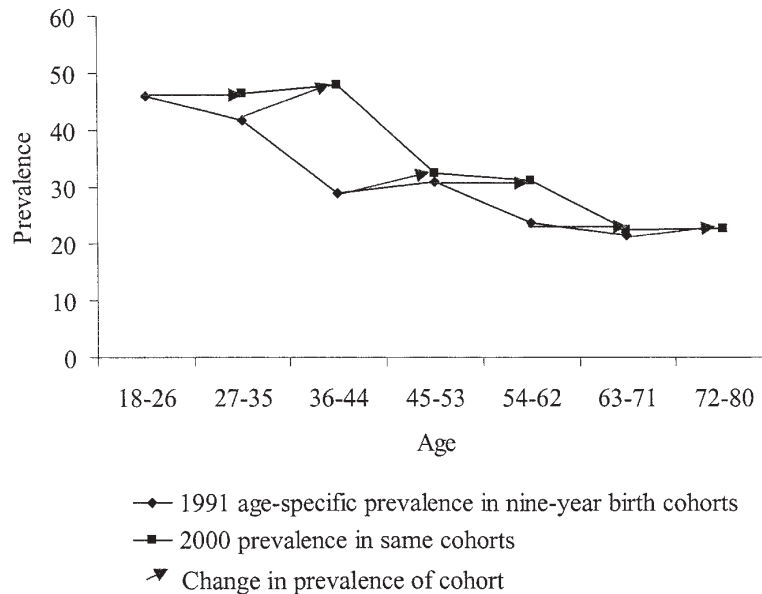


FIG 1. Prevalence of allergen skin sensitization by age stratification.

TABLE II. Skin test responses with 2 different manufacturers' allergen solutions

Allergen	Solutions used in 1991, mm (mean $\pm$ SD)	Solutions used in 2000, mm (mean $\pm$ SD)	P value*	No. that concur†	No. that disagree†	K Value
<i>D pteronyssinus</i>	3.5 $\pm$ 2.3	3.4 $\pm$ 2.5	.32	53	8	0.80
Cat fur	3.0 $\pm$ 2.6	3.4 $\pm$ 3.1	.03	58	3	0.92
Grass pollen	4.2 $\pm$ 3.0	4.2 $\pm$ 3.2	.75	58	3	0.92

*P value obtained by using the paired *t* test on the difference between the mean wheal diameters.

†Values relate to a response of greater than or equal to 3 mm in mean diameter.

RR of 1.92 and 95% CI of 1.35 to 2.79; age 36-44 years, RR of 1.36 and 95% CI of 0.95 to 1.95; age 45-53 years, RR of 1.45 and 95% CI of 1.02 to 2.07; and age 54-62 years, RR of 1.14 and 95% CI of 0.68 to 1.92. There was no cross-sectional relationship between allergen skin sensitization and sex or smoking status in either 1991 or 2000 and no relation between change in sensitization to cat fur and change in cat ownership between 1991 or 2000. Sensitization to any allergen tended to be more common in socioeconomically advantaged groups in both 1991 and 2000 and significantly so in 2000 (Table III).

Skin sensitization to allergens in 1991 was generally a strong predictor of sensitization in 2000. The positive predictive value of sensitization in 1991 for sensitization in 2000 was 78% for any allergen, 70% for *D pteronyssinus*, and 82% for mixed grasses, but only 38% for cat fur. Negative predictive value for any allergen was 89%, 91% for *D pteronyssinus*, 96% for mixed grasses, and 97% for cat fur. Incident sensitization to any allergen between 1991 and 2000 occurred in 11.5% of those with negative reactions to all allergens in 1991, predominantly to *D pteronyssinus* (8.7%), with no clear trend in relation to age (Table IV). Complete resolution of sensitization between 1991 and 2000 occurred in 21.8% of those with

sensitization to any allergen, and although the proportion with resolution during the study period tended to be higher in older age groups, the absolute numbers of individuals with resolved and incident sensitization in these age groups were approximately similar (Table IV). As a result, the overall prevalence of sensitization remained constant in the older age groups and increased slightly in those aged less than 44 years in 1991. Fig 1 shows the cross-sectional and longitudinal relationship between age groups and birth cohorts over the 9 years. There was no significant within-subject change from 1991 to 2000 (adjusted odds ratio, 1.07; 95% CI, 0.97-1.19), but there was a significant birth cohort effect, such that successively younger 9-year birth cohorts had a higher prevalence of allergen skin sensitization (adjusted odds ratio, 1.27; 95% CI, 1.18-1.37). As a result of this cohort effect, the prevalence of allergic sensitization has increased in this general adult population sample.

DISCUSSION

This study has confirmed the previously reported cross-sectional relationship between increasing age and decreasing allergen skin sensitivity^{1,2,4-6,9,17-20} in 2 cross-section-

TABLE III. The effect of age, sex, smoking, social class, and season seen on the prevalence of allergen skin sensitization

	1991 % prevalence					2000 % prevalence				
	N	Any	Dust	Cat fur	Grass	N	Any	Dust	Cat fur	Grass
Overall	1339	30.5	17.2	17.0	18.8	1339	31.8	19.2	9.3	18.6
Age group										
18-26	87	46.0	26.4	27.6	36.8	0	0	0	0	0
27-35	180	41.7	27.8	30.0	25.0	84	46.4	33.3	14.3	35.7
36-44	323	29.1	18.0	17.7	19.5	171	48.0	32.3	18.7	28.1
45-53	331	31.1	16.0	16.0	17.8	318	32.4	19.5	10.7	22.0
54-62	278	23.7	10.1	11.2	13.3	336	31.3	19.6	9.2	16.4
63-71	140	21.4	12.9	7.1	11.4	285	22.5	11.6	3.9	10.9
72-80	0	0	0	0	0	145	22.8	9.0	3.5	10.3
<i>P</i> value for trend*		<.001	<.001	<.001	<.001		<.001	<.001	<.001	<.001
Sex										
Male	666	32.4	18.0	17.0	19.1	666	31.8	19.2	8.3	18.3
Female	673	28.5	16.3	17.2	18.6	673	31.8	19.2	10.4	18.9
<i>P</i> value*		.038	.205	.540	.129		.407	.409	.393	.468
Smoking status										
Never	711	31.4	16.9	18.6	21.7	676	33.6	20.9	10.1	21.0
Exsmoker	389	28.8	16.7	14.9	15.7	510	30.4	17.1	8.6	16.5
Current	239	30.5	18.8	16.3	15.5	153	28.8	19.0	8.5	15.0
<i>P</i> value for trend*		.836	.216	.558	.049		.953	.992	.635	.416
Social class†										
I	246	32.1	18.7	18.7	21.5	174	42.4	26.7	12.2	26.2
II	436	31.0	17.2	18.1	18.6	455	34.3	19.3	10.8	20.6
IIINM	295	30.2	16.1	15.3	20.3	350	26.4	15.2	9.2	15.8
IIIM	259	29.0	16.2	14.3	15.8	255	28.4	18.9	7.1	15.8
IV and V	34	20.6	17.7	20.6	5.9	36	19.4	13.9	0	5.6
<i>P</i> value for trend*		.216	.334	.285	.108		.003	.093	.077	.008

**P* values adjusted for age, sex, smoking status, social class, and period of measurement.

†I, Professional; II, intermediate; IIINM, skilled nonmanual; IIIM, skilled manual; IV, semiskilled manual; V, unskilled manual.

TABLE IV. The effect of age in 1991 on the persistence and resolution of a positive reaction and the incidence of allergen skin sensitization

	Incident reaction in 2000*				Resolved reaction in 2000†			
	Any, n (%)	<i>D pteronyssinus</i> , n (%)	Cat fur, n (%)	Grass, n (%)	Any, n (%)	<i>D pteronyssinus</i> , n (%)	Cat fur, n (%)	Grass, n (%)
Overall	107 (12)	96 (9)	37 (3)	47 (4)	89 (22)	96 (9)	37 (3)	47 (4)
Age group in 1991								
18-26	4 (9)	7 (11)	3 (5)	3 (6)	3 (8)	7 (11)	3 (5)	3 (6)
27-35	13 (12)	13 (10)	3 (2)	7 (5)	8 (11)	13 (10)	3 (2)	7 (5)
36-44	29 (13)	25 (9)	12 (5)	17 (7)	16 (17)	25 (9)	12 (5)	17 (7)
45-53	26 (11)	27 (10)	13 (5)	10 (4)	27 (26)	27 (10)	13 (5)	10 (4)
54-62	16 (8)	15 (6)	4 (2)	5 (2)	18 (27)	15 (6)	4 (2)	5 (2)
63-71	19 (17)	9 (7)	2 (2)	5 (4)	17 (57)	9 (7)	2 (2)	5 (4)
<i>P</i> value for trend	.760	.123	.132	.078	<.001	.123	.132	.078

*As a percentage of those that had a negative reaction in 1991.

†As a percentage of those that had a positive reaction in 1991.

al analyses of the same cohort at different times. The incidence and resolution data within age groups suggest that the increase was due primarily to a persistence of 1991 levels of sensitization prevalence within all age cohorts, as opposed to the within-cohort decline in prevalence expected from the cross-sectional relationship between age and sensitization. This suggests that the main explanation for the cross-sectional relationship of decreased sensitization with increasing age is a cohort effect from a higher prevalence

in young people rather than an aging effect. Consistent with previous reports,^{18,27} we found no evidence of higher mortality in sensitized individuals. We also found no appreciable effects of sex or smoking on the prevalence of allergen skin sensitization, but there was a trend toward a higher prevalence of sensitization in the higher occupational social classes, which was significant in this study in 2000 and was also significant in cross-sectional analysis of the total population from 1991.²⁸

The initial study sample was selected at random from the electoral register of a district of Nottingham, encompassing adult subjects with a broad range of ages across the social classes and living in a spectrum of urban and rural areas. Although we were able to study only 51% of the initial participants in the present study, there was no evidence of bias in participants in the 2000 study in relation to their allergen skin sensitization status in 1991. Proportionally fewer of the 18- to 35-year-old subjects in the 1991 study participated in 2000, predominantly because of relocation, but there was no difference in allergen skin sensitization between those participating in the 1991 and 2000 studies and those lost to follow-up, even when analyzed in 9-year age strata. Individuals with a lower occupational socioeconomic status were underrepresented in our sample, and because lower socioeconomic status was associated with a lower prevalence of allergen skin sensitization in this study, this may have led to an overestimate of the total prevalence of sensitization relative to the general population.

Although the allergen solutions used in the 2 studies were produced by different manufacturers, the agreement between responses to the 2 solutions was high, making it unlikely that the use of different solutions significantly biased our findings. In particular, the decline in prevalence of cat fur sensitization seen between 1991 and 2000 cannot be explained by the use of different solutions because the solution used in 2000 produced a slightly and statistically significantly larger mean wheal response than that used in 1991. The reason for the decline in cat fur sensitization is not clear but was not due to any change in cat ownership between studies.

The proportion of self-reported current smokers was low in our original sample and decreased between 1991 and 2000 (Table I), possibly as a result of selection bias but also as a result of a 43% self-reported cessation rate between the 2 studies. However, adjustment for smoking status did not significantly alter allergen skin sensitization results. Inconsistent associations have previously been reported between smoking status and allergen skin sensitization, with several,¹³⁻¹⁶ but not all,^{2,6} studies suggesting that current smokers have a lower prevalence of sensitization compared with that of subjects who had never smoked. We found no association between smoking status and sensitization in our population. The lack of association between sex and allergen skin sensitization seen in our data is consistent with the findings of general population samples.^{2,4,6,13}

Our finding of evidence that there is a higher prevalence of allergic sensitization in younger cohorts is consistent with the study by Barbee et al,¹³ which also suggested that the higher prevalence of sensitization in younger people is a cohort effect rather than an age effect. We therefore conclude that the prevalence of allergen skin sensitization is increasing in the general population as a result of a secular trend of increasing allergic sensitization in successive birth cohorts. The cause or causes of this trend are not clear.

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