

# Change in prevalence of IgE sensitization and mean total IgE with age and cohort

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**Background:** Cross-sectional studies show that the prevalence of IgE sensitization is lower in older age groups than younger age groups. This could reflect either a decrease in sensitization with aging or a higher prevalence of sensitization in more recent birth cohorts.

**Objective:** To assess change in IgE sensitization and mean total IgE in young adults as they age.

**Methods:** Serum specific IgE to common allergens and total IgE were measured on 2 occasions about 9 years apart in 6371 young adults living in 28 centers, mainly in Western Europe, who took part in the European Community Respiratory Health Survey II. Outcomes were analyzed by using generalized estimating equations, and adjustments were made for differences between laboratory measures on the 2 occasions.

**Results:** Overall, there was no net change in the prevalence of sensitization to at least 1 of house dust mite, grass, or cat (net change per 10 years of follow-up,  $-0.1\%$ ; 95% CI,  $-1.7\%$  to  $1.5\%$ ), although there was a fall in mean total IgE (ratio of geometric mean total IgE, 0.86; 95% CI, 0.79 to 0.93). There was evidence that sensitization to at least 1 allergen was higher in more recent cohorts, and this was largely explained by a higher prevalence of sensitization to grass.

**Conclusion:** The disease burden associated with IgE sensitization in adults, and particularly with IgE sensitization to grass, is likely to continue to increase for some time despite current evidence that the increase in allergy seen in children may have ceased. (*J Allergy Clin Immunol* 2005;116:675-82.)

**Key words:** ECRHS, atopy, total IgE, cohort

There is now substantial evidence for an increase in IgE sensitization to common allergens. Several repeated cross-sectional surveys in children<sup>1-4</sup> and adults<sup>5-8</sup> have shown increases in the age-specific prevalence of sensitization measured by skin tests or as the presence of serum specific IgE. This increase has not been restricted to 1 particular allergen but is seen for sensitization to house dust mite, grasses, pollens, and animal danders.<sup>1-6</sup> There has been an increase in the prevalence of sensitization to at least 1 allergen and an increase in the prevalence of sensitization to more than 1 allergen (polysensitization). When changes in the prevalence of IgE sensitization in teenagers and adults have been studied within a single study, the increases observed over time have generally been higher for teenagers than adults.<sup>8</sup> Changes in total IgE have not been widely reported, but no change in total IgE has occurred in Greenland, despite substantial increases in the age-sex-specific prevalence of IgE sensitization to inhalant allergens.<sup>8</sup>

In cross-sectional studies of adults, younger adults have a higher prevalence of sensitization than older adults. This has generally been interpreted as reflecting a decline in IgE

#### Abbreviation used

ECRHS: European Community Respiratory Health Survey

sensitization with age. Longitudinal studies in Tucson,<sup>9</sup> Nottingham,<sup>10</sup> Copenhagen,<sup>11</sup> and a sample of French policemen<sup>12</sup> each suggested that sensitization increased with age, although in the latter 3, this was not so apparent after 45 years of age. In Tucson,<sup>9</sup> Nottingham,<sup>10</sup> and Copenhagen,<sup>11</sup> the cross-sectional association of young age with a higher prevalence of sensitization was considered more likely to reflect a cohort effect and not an aging effect. Changes in total IgE as cohorts age have not been widely reported, but levels appear stable over an 8-year period in adults.<sup>12,13</sup>

Few longitudinal studies have reported changes in IgE sensitization in adults by using serum specific IgE, and few that have considered changes in total IgE in the same population. The European Community Respiratory Health Survey (ECRHS) II is a multicenter, international study in which representative community-based samples of young adults have had their atopic status assessed on 2 occasions about 8 years apart using serum specific IgE. One of the stated aims of the study is to identify environmental risk factors for the development of IgE sensitization in adult life. In this report, we assess the changes in IgE sensitization and in total IgE in a cohort of people living in 28 centers and 13 countries over a period of approximately 8 years, and we consider the implications of our findings for predicting the course of the current epidemic of allergy in the mainly European participating centers.

## METHODS

### Study subjects

The methods for ECRHS I and ECRHS II have been published in more detail elsewhere,<sup>14,15</sup> and further information is available from the study Web site ([www.ecrhs.org](http://www.ecrhs.org)).

In ECRHS I, participating centers were each selected as an area defined by pre-existing administrative boundaries with a population of at least 150,000 people. A community-based sampling frame was used to select randomly at least 1500 men and 1500 women age 20 to 44 years, who were sent a short postal questionnaire. A random sample of responders was selected to take part in stage II, during which the responders were invited to visit a local testing center, answer a more detailed administered questionnaire, and provide a blood sample for measurement of specific IgE and total IgE. In most centers, a further sample of symptomatic subjects was also invited to participate. These subjects are not included in this analysis.

### Study design

Twenty-eight centers that participated in ECRHS I stage II took part in ECRHS II,<sup>15</sup> including blood sampling for measurement of specific IgE and total IgE. Participants in ECRHS I who responded to stage II (defined as participants who provided at least data on smoking at stage II) were eligible for ECRHS II. From 1998 to 2002 (depending on center), eligible participants completed the short symptoms questionnaire and were then invited to a local testing center where, as before, they answered a more detailed administered

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questionnaire and provided a blood sample for measurement of specific IgE and total IgE.

### Laboratory methods

During both surveys, blood samples were handled in a similar manner and analyzed in a central laboratory (Pharmacia Uppsala in 1992 and Kings College London in 2002). Blood samples were centrifuged and serum stored at  $-20^{\circ}\text{C}$  until analysis. On both occasions, the Pharmacia CAP system (Uppsala, Sweden) was used.

### Standardization of laboratory methods in 2 surveys

Duplicate serum samples from 794 British subjects tested in 1992 (in Uppsala) were stored at  $-20^{\circ}\text{C}$ . In 2002, these samples were analyzed in the laboratory in London. Samples were considered positive if specific IgE was greater than 0.35 kU/L, but similar calculations were made by using a higher cutoff of 0.70 kU/L. The difference in the prevalence of IgE sensitization in the 794 samples as measured in 1992 and in 2002 was calculated, and appropriate SEs for the difference (referred to in this article as *laboratory bias*) were derived considering the data as matched pairs. Similarly, the mean difference and SE for measures of total IgE in 1992 and 2002 (in the 794 samples) were calculated on the log scale. Poor agreement between the 2 measures for *Cladosporium* ( $\kappa$ , 0.69; prevalence in first assessment, 5.67%, and in second assessment, 4.28%) was observed, and sensitization to *Cladosporium* was not considered further (see Tables E1 and E2 in the Online Repository in the online version of this article at [www.mosby.com/jaci](http://www.mosby.com/jaci)).

### Statistics

Absolute change in the prevalence of sensitization to each allergen and to sensitization to at least 1 allergen per 10 years of follow-up was estimated by using population-averaged generalized estimating equations for a binomial outcome with identity link, with participants identified as the clustering factor and length of follow-up as an independent variable. The laboratory bias was subtracted from the observed net change, and the appropriate SE for the laboratory-corrected value was determined, taking into account the variance of both the change and the bias and the length of follow-up. Estimates from each center were examined for heterogeneity, and when present, they were combined by using random effects meta-analysis.<sup>16</sup>

To examine the association of age with the absolute changes observed, participants were divided into 4 age groups (<27.5 years, 27.5 to <35 years, 35 to <42.5 years, 42.5 years and above). These age groups were chosen because there were sufficient participants in each group in most centers to allow change to be determined by using either center adjusted or country-adjusted generalizing estimating equations. For these analyses, change was standardized for a 7½-year period of follow-up so that differences in age-specific prevalence at each survey and possible cohort effects could be explored. For these purposes, the prevalence of sensitization in the second survey in each age group was determined by applying the appropriate laboratory-corrected country-adjusted change over a period of 7.5 years to the observed baseline prevalence.

Overall mean change in log total IgE per 10 years of follow-up was determined by using regression analyses with correction for laboratory bias, and change in each age group for 7.5 years of follow-up was determined in a similar manner.

Analysis was performed by using Stata 8.2.<sup>17</sup>

### RESULTS

A total of 6137 subjects (52.3 %) of the 11,719 subjects who provided a blood sample in the first survey took

**TABLE I.** Net change in sensitization to house dust mite, grass, and cat and total IgE

|                                    | Prevalence<br>(%) in<br>1992 | Net change<br>(95% CI)<br>per 10 y of<br>follow-up* | P value for<br>heterogeneity<br>between<br>centers |
|------------------------------------|------------------------------|-----------------------------------------------------|----------------------------------------------------|
| House dust mite                    |                              |                                                     |                                                    |
| (>0.35 kU/L)                       | 17.1                         | -1.1 (-2.4 to 0.2)                                  | $P < .001$                                         |
| (>0.70 kU/L)                       | 13.0                         | -0.2 (-0.9 to 0.6)                                  | $P = .165$                                         |
| Grass                              |                              |                                                     |                                                    |
| (>0.35 kU/L)                       | 18.2                         | 0.3 (-0.9 to 1.6)                                   | $P < .001$                                         |
| (>0.70 kU/L)                       | 14.8                         | -0.7 (-1.6 to 0.1)                                  | $P = .017$                                         |
| Cat                                |                              |                                                     |                                                    |
| (>0.35 kU/L)                       | 9.1                          | -1.7 (-2.6 to -0.8)                                 | $P = .038$                                         |
| (>0.70 kU/L)†                      | 6.4                          | -0.5 (-1.1 to 0.1)                                  | $P = .497$                                         |
| House dust mite<br>or grass or cat |                              |                                                     |                                                    |
| (>0.35 kU/L)                       | 29.8                         | -0.1 (-1.7 to 1.5)                                  | $P < .001$                                         |
| (>0.70 kU/L)                       | 24.4                         | -0.7 (-1.6 to 0.2)                                  | $P = .207$                                         |
|                                    |                              | <b>Ratio of geometric<br/>mean</b>                  |                                                    |
| Total IgE (kU/L)                   | 29.5                         | 0.86 (0.79 to 0.93)                                 | $P < .001$                                         |

\*With correction for laboratory bias with estimates generated from generalized estimating equations conducted center by center with estimates combined by using random effect meta-analysis.

†Standardized cutoffs used to determine sensitization at each survey with estimates generated from generalized estimating equations conducted center by center with estimates combined by using random effect meta-analysis.

part in ECRHS II and went on to provide a sample in the second. There was variation in the response between centers (minimum, 25.2% in Bordeaux; maximum, 82.4% in Reykjavik). Overall response rates were lower in younger subjects, subjects with symptoms, and subjects who reported smoking at baseline, with no significant ( $P > .05$ ) variation in these patterns between centers (see Table E3 in the Online Repository in the online version of this article at [www.mosby.com/jaci](http://www.mosby.com/jaci)). Being sensitized to an allergen in the first survey was not significantly ( $P > .05$ ) associated with response to the second survey. Length of follow-up was variable between centers, ranging from a center median of 5.0 years in Melbourne to 10.5 years in Caerphilly, with an overall median of 8.9 years.

### Net change in sensitization and total IgE

Table I shows the laboratory-corrected net change in prevalence of IgE sensitization to each of the allergens standardized to a 10-year period of follow-up. There was no significant overall change in the prevalence of IgE sensitization to house dust mite or grass or to at least 1 allergen by using either the low or the higher cutoff values. Sensitization to cat showed an overall decrease. There was evidence of heterogeneity for each of these estimates, with no clear geographical pattern in the variation observed (Fig 1). For sensitization to at least 1 allergen, Montpellier and Barcelona were outliers, with Barcelona showing a decrease (net change,  $-11.6\%$ ; 95% CI,  $-20.2\%$  to  $-3.0\%$ ) and Montpellier showing an increase (net change,  $8.4\%$ ; 95% CI,  $2.6\%$  to  $14.2\%$ ).

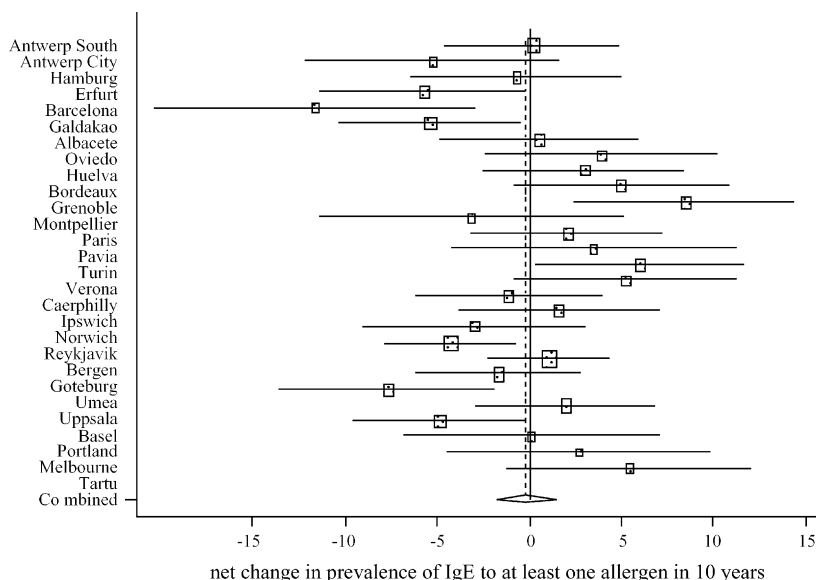


FIG 1. Net change in prevalence of sensitization to at least 1 allergen per 10 years of follow-up.

There was an overall decrease in total IgE (ratio of geometric means over 10-year period of follow-up, 0.86; 95% CI, 0.79 to 0.93). Substantial variation between the centers in the magnitude and direction of this change was observed (test for heterogeneity,  $P < .001$ ; Fig E1).

### Association of net change with age

In the first survey, the prevalence of sensitization to house dust mite, grass, and at least 1 allergen was higher in younger age groups than older age groups (Table II). There were no significant differences in the change in sensitization to each allergen between age groups, although the general pattern was for older age groups to show a greater decrease (or less marked increase) during the period of follow-up. There was a significant difference between age groups in the net change in prevalence of sensitization to at least 1 allergen by using the higher cutoff ( $<0.70$  kU/L), with the youngest age group showing small increases and the oldest age group showing a significant decrease. The estimates for the higher cutoff could not be fully adjusted for the area in which the study was conducted and were adjusted for country rather than center because of the small numbers of subjects in some age groups in several centers. For similar reasons, change in sensitization to cat has not been considered in Table II.

Figs 2 and 3 display the change in sensitization to grass and house dust mite by age and birth cohort, and Fig 4 shows the change in prevalence of sensitization to at least 1 allergen, using the low cutoff ( $<0.35$  kU/L). These graphs have been generated from the data displayed in Table II.

At each age, sensitization to grass was higher in the later birth cohorts than in the earlier cohorts (Fig 2). This apparent cohort effect was not observed for sensitization to house dust mite (Fig 3). The age-specific prevalence

of sensitization to at least 1 allergen showed a cohort effect similar to that of grass (Fig 4), and this was unchanged by choosing a cutoff point of 0.70 kU/L (data not shown).

In each survey, total IgE was higher in younger subjects than older subjects. The decline in total IgE over the period of follow-up was greatest in the youngest group of subjects (Table II), and the greater decline in younger subjects showed no significant variation between centers ( $P$  for heterogeneity,  $<.2$ ). In contrast with specific IgE to grass and to sensitization to any allergen, there was little evidence for an increase in total IgE with successive birth cohorts (Fig 5).

### DISCUSSION

This large multicenter study examined changes in serum specific IgE in young and middle-aged adults. There was no significant change in the prevalence of being sensitized to at least 1 environmental allergen over a 10-year period. There was some evidence that the prevalence of sensitization to at least 1 allergen decreased more in the older age groups than in the younger age groups, but these age-related changes were small in comparison with the differences between cohorts. More recent birth cohorts had a higher prevalence of sensitization to at least 1 allergen than earlier cohorts, which was associated with cohort-related increases in sensitization to grass. No cohort effect was observed for house dust mite or for total IgE.

Changes in reagents, staff, and laboratory methods for the assessment of sensitization may lead to an overall bias in the estimation of change over time. In each survey, samples were handled in a similar manner following a specified protocol, and we have adjusted our estimates for

**TABLE II.** Net change in sensitization over a period of 7.5 years by age group\*

|                                                | Under 27.5 y<br>(n = 1316) | 27.5 to <35 y<br>(n = 1789) | 35 to <42.5 y<br>(n = 2094) | 42.5 y and above<br>(n = 937) | P†      |
|------------------------------------------------|----------------------------|-----------------------------|-----------------------------|-------------------------------|---------|
| House dust mite (0.35 kU/L)                    | −0.6 (−2.4 to 1.2)         | −1.5 (−3.3 to 0.3)          | −1.1 (−2.9 to 0.7)          | −2.3 (−4.8 to −0.5)           | P = .58 |
| Baseline prevalence                            | 19.4                       | 18.8                        | 14.5                        | 16.6                          |         |
| Grass (0.35kU/L)                               | 1.7 (−0.1 to 3.5)          | 0.1 (−1.7 to 1.5)           | 0.2 (−1.3 to 0.8)           | −0.3 (−2.4 to 1.8)†           | P = .14 |
| Baseline prevalence                            | 23.3                       | 19.2                        | 16.7                        | 12.6                          |         |
| House dust mite or<br>grass or cat (0.35 kU/L) | 0.7 (−1.5 to 2.9)          | −0.6 (−2.5 to 1.3)          | 0.1 (−1.4 to 1.6)           | −1.2 (−3.2 to 0.7)            | P = .36 |
| Baseline prevalence                            | 34.6                       | 32.2                        | 27.1                        | 24.8                          |         |
| Any high cutoff (0.70 kU/L)                    | 0.1 (−1.5 to 1.7)          | −1.1 (−2.5 to 0.3)          | −0.7 (−2.1 to 0.7)          | −2.9 (−4.3 to −1.5)           | P = .01 |
| Baseline prevalence                            | 30.1                       | 27.1                        | 21.0                        | 19.0                          |         |
| Ratio of geometric<br>mean of total IgE        | 0.84 (0.77 to 0.91)        | 0.90 (0.84 to 0.97)         | 0.91 (0.85 to 0.97)         | 0.91 (0.85 to 0.98)           | P = .04 |
| Geometric mean (kU/L) at baseline              | 32.4                       | 29.5                        | 26.9                        | 28.1                          |         |

\*Estimates for house dust mite sensitization and for sensitization to any allergen with a high cutoff generated from country-adjusted generalized estimating equations (no between country heterogeneity observed). Estimates for grass sensitization and sensitization to any allergen with 0.35 kU/L cutoff generated from generalized estimating equations performed country by country and combined by using random effects meta-analysis.

†Belgium dropped from analysis because no subject within this age group IgE-sensitized to grass in ECRHS I or in ECRHS II.

‡Significance of age group and length of follow-up interaction term tested by Wald statistic in country-adjusted generalized estimating equation (reflecting whether significant differences between age groups in net change).

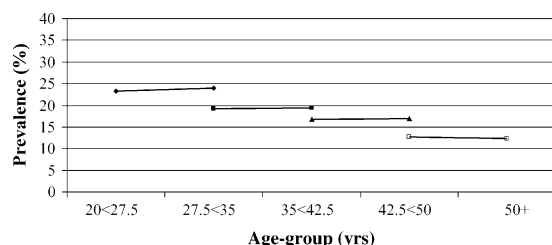


**FIG 2.** Age cohort prevalence of sensitization to grass in ECRHS I and ECRHS II (◆-, born 1965 or later; ■-, born 1958-1964; ▲-, born 1951-1957; □-, born 1950 or earlier).

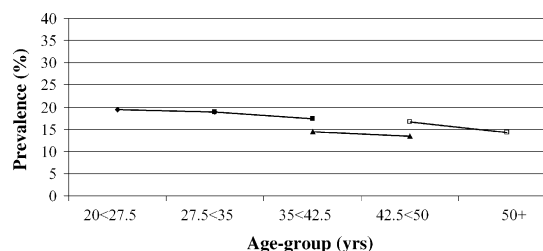


**FIG 3.** Age cohort prevalence of sensitization to house dust mite in ECRHS I and ECRHS II (◆-, born 1965 or later; ■-, born 1958-1964; ▲-, born 1951-1957; □-, born 1950 or earlier).

any bias that could have been introduced by changes in laboratory reagents. Responders to the second survey were less likely to be IgE-sensitized than people who did not take part, but this difference should not influence the internal validity of the study.

Two earlier studies<sup>9,10</sup> each studied changes in IgE sensitization over an 8-year or 9-year period in adults by using skin prick tests. These studies examined a larger age range than in the ECRHS, and each study was limited to a single area. They suggested minimal changes in sensitization with age in adults and an increase in IgE sensitization with successive cohorts. Broadfield et al<sup>10</sup> presented unadjusted changes in prevalence of sensitization to individual allergens, and the changes with aging and between cohorts appeared similar for all allergens. The analyses could not be adjusted for variations in skin test reagents or practice over time. Linneberg et al<sup>11</sup> studied IgE sensitization to any 1 of 6 allergens by using serum specific IgE in about 600 adults age 15 to 69 years in 1990 and again in 400 responders to follow-up 8 years later. Their data supported a cohort effect on sensitization. The prevalence of IgE sensitization and the implied magnitude of the age-related changes that occurred in

the Copenhagen study were much greater than in the Scandinavian centers in the ECRHS or than in the ECRHS overall, but individual allergens were not considered, nor was total IgE. Our study, which includes a larger number of subjects in more than 1 geographical area, adds to the information provided in these earlier reports.

We confirm that there is little change in IgE sensitization to at least 1 allergen in this age group as they grow older. We have corrected our estimates to allow for overestimation or underestimation of change in sensitization that could be attributed to change in laboratory reagents and have used generalized estimating equations, a statistical approach that is more robust to this measurement error than estimates of incidence or remission. This statistical approach is the most appropriate for repeated measures and permits adjustment for the variable length of follow-up of subjects. However, because net change in sensitization is low, for some analyses the approach limits the extent to which all confounders can be incorporated, and in some analyses, we have had to consider our data grouped by country rather than by the sampling unit (center). The season in which blood samples were taken was not associated with sensitization at baseline, and it is

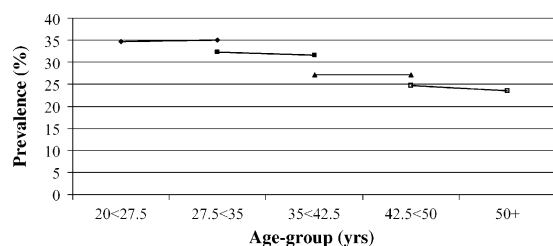


**FIG 4.** Age cohort prevalence of sensitization to any allergen ( $>0.35$  kU/L) in ECRHS I and ECRHS II (—♦—, born 1965 or later; —■—, born 1958–1964; —▲—, born 1951–1957; —□—, born 1950 or earlier).

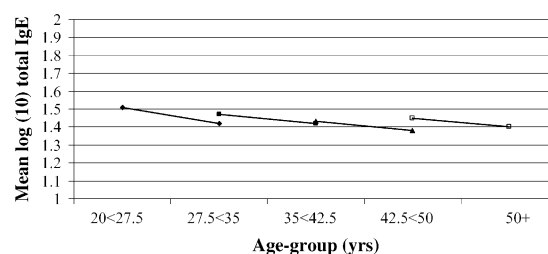


**FIG 5.** Age cohort geometric mean total IgE in ECRHS I and ECRHS II (—♦—, born 1965 or later; —■—, born 1958–1964; —▲—, born 1951–1957; —□—, born 1950 or earlier).

unlikely that inability to adjust for this explains our findings.

There was a small but significant decrease in sensitization to cat, and the small observed decrease in sensitization to house dust mite only just failed to reach significance. This decrease is more marked in the older age groups, and had we studied a wider age range, it is possible that we may have seen evidence of both a cohort and aging effect in the older adults. Exposure to both house dust mite and cat can be modified by changes in individual behavior. More detailed analyses of the data available in the ECRHS will be required to explore whether allergen avoidance is a plausible explanation for our findings, but even for a study as large as the ECRHS, the power to detect associations of modification of lifestyle with such small changes in sensitization will be limited.

Successive cohorts have a higher prevalence of sensitization to grass and, possibly as a consequence, to at least 1 allergen. Our observation that IgE sensitization increases with successive cohorts is consistent with results from both repeat cross-sectional studies and the limited number of longitudinal studies, but the observation that this is explained by increases in grass sensitization is at odds with previous work. Repeated cross-sectional studies have suggested that there have been increases in sensitization to all allergens, not just increases to grass. In children in Grabs,<sup>1</sup> Northern Japan,<sup>2</sup> Leipzig,<sup>3</sup> Viterbo,<sup>4</sup> and Wagga Wagga,<sup>18</sup> there was no evidence that the temporal increase in sensitization to grass or pollens was greater than for mites, and in adults in Nottingham, the cohort effect was apparent for both house dust mite and grass.<sup>10</sup> However, in children in Leipzig,<sup>3</sup> it was striking that the temporal increase in sensitization to pollen (from 14% to 21.5%) was of the same magnitude as the increase in sensitization to at least 1 allergen (19.3% to 26.7%), unlike the increase in sensitization to mites (4.6% to 8.1).

Our article also shows that total IgE declines with age, and there is no evidence of a cohort-related increase. The observation of lower total IgE in older subjects compared with younger subjects that has been reported in cross-sectional studies<sup>19,20</sup> can, according to our data, be interpreted as reflecting an age-related decline. Although IgE sensitization and total IgE are both associated with an increased risk of allergic disease in individuals, they exhibit very different changes with aging and with cohort.

This may reflect their differing association with environmental factors, such as family size and birth order<sup>21–23</sup> and smoking.<sup>24–26</sup>

Substantial variation between centers was observed in the changes for all allergens. Because of the small amount of change in sensitization, it is technically difficult to explore reasons for the variations between centers and countries while controlling for many confounders. However, we are able to conclude that no clear or consistent geographical pattern has emerged, and centers that show a high net change in sensitization to 1 allergen do not necessarily show a high net change in another. There was no evidence that the English-speaking centers with a high baseline prevalence of sensitization<sup>27</sup> had a lower (or higher) net change compared with Southern Europe, which had a low baseline prevalence. There may be some between-center variation in cohort effect, but we have insufficient data to explore this, and our broad conclusions remain the same.

In children, there have been reports suggesting that the trend in increasing prevalence of conditions associated with IgE sensitization has begun to fall, or at least flatten out.<sup>28–30</sup> The implications of our analysis is that even were this to be the case, the prevalence of IgE sensitization in the population is set to rise for many years to come, and the burden of this will fall increasingly on an older population. Even if there were effective primary prevention interventions to reduce sensitization in children, the prevalence of IgE sensitization in the adult population of Western Europe is likely to increase until the middle of the century. Public health and clinical services to meet the needs of these adults will need to be identified and provided. Services for those with allergic diseases that are associated with sensitization to grass may require particular attention. We have already presented data from ECRHS I that support a cohort-related increase in the incidence of asthma in our study population,<sup>31</sup> and data to examine this for hayfever and nasal allergies have been collected in ECRHS II.

In conclusion, in a large multinational cohort of young to middle-aged adults, there was little change in the prevalence of specific IgE of sensitization to at least 1 allergen. The age-specific prevalence of sensitization to at least 1 allergen in more recent cohorts was higher than in the earlier cohorts, and this was associated with a

cohort-related increase in sensitization to grass. Our work strongly suggests that the disease burden within our adult populations in Western Europe is likely to continue for some years, despite growing evidence that the increase in childhood allergy may have ceased.

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