Changes in IgE sensitization and total IgE levels over 20 years of follow-up

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Background: Cross-sectional studies have reported a lower prevalence of sensitization in older adults, but few longitudinal studies have examined whether this is an aging or a year-of-birth cohort effect.

Objective: We sought to assess changes in sensitization and total IgE levels in a cohort of European adults as they aged over a 20-year period.

Methods: Levels of serum specific IgE to common aeroallergens (house dust mite, cat, and grass) and total IgE levels were measured in 3206 adults from 25 centers in the European Community Respiratory Health Survey on 3 occasions over 20 years. Changes in sensitization and total IgE levels were analyzed by using regression analysis corrected for potential differences in laboratory equipment and by using inverse sampling probability weights to account for nonresponse.

Results: Over the 20-year follow-up, the prevalence of sensitization to at least 1 of the 3 allergens decreased from 29.4% to 24.8% (−4.6%; 95% CI, −7.0% to −2.1%). The prevalence of sensitization to house dust mite (−4.3%; 95% CI, −6.0% to −2.6%) and cat (−2.1%; 95% CI, −3.6% to −0.7%) decreased more than sensitization to grass (−0.6%; 95% CI, −2.5% to 1.3%). Age-specific prevalence of sensitization to house dust mite and cat did not differ between year-of-birth cohorts, but sensitization to grass was most prevalent in the most recent ones. Overall, total IgE levels decreased significantly (geometric mean ratio, 0.63; 95% CI, 0.58-0.68) at all ages in all year-of-birth cohorts.

Conclusion: Aging was associated with lower levels of sensitization, especially to house dust mite and cat, after the age of 20 years. (J Allergy Clin Immunol 2016;137:1788-95.)

Key words: Allergens, sensitization, cohort study, epidemiology, IgE, longitudinal analysis, aging, immunosenescence

Population-based cross-sectional studies have shown that the prevalence of sensitization is higher in younger than in older age groups. 1-4 Although there have been year-of-birth cohort-related increases in atopy over the last decades, it is hypothesized that these cross-sectional observations might reflect decreases in sensitization with aging-related immunosenescence. Longitudinal studies that have performed skin prick tests or measured serum allergen-specific IgE levels at baseline and follow-up over periods of up to 14 years have reported that sensitization increased with aging, although changes were less evident in middle-aged and older adults. 5-7 Two recent longitudinal studies
reported no change or a slight decrease in sensitization with aging.4–8 In one of these studies, changes in sensitization were based on allergen-specific IgE measures,8 whereas in the other the comparison between time points was based on both specific IgE levels and skin prick test responses.3

Within the European Community Respiratory Health Survey (ECRHS),3 a multicenter cohort study of more than 6000 young and middle-aged adults followed for a 10-year period, there was little evidence of substantial change in sensitization to at least 1 of cat, grass, or house dust mite (as measured based on serum specific IgE levels) over time as the cohort aged. The age-specific prevalence of sensitization to grass but not to the other allergens measured was higher in more recent year-of-birth cohorts. At the time, it was observed that changes in laboratory methods between baseline and follow-up could influence assessment of change in sensitization; such biases are even more difficult to quantify when using skin prick tests.

Completion of the third phase of the ECRHS has allowed assessment of serum specific IgE levels on 3 occasions: baseline and 10- and 20-year follow-up. The aims of this report were to (1) assess the changes in IgE sensitization and total IgE levels in this population-based cohort of European adults over a period of 20 years and (2) to investigate whether these changes were different between year-of-birth cohorts.

METHODS

Study participants

This is a multicenter population-based cohort study. Detailed descriptions of the methods for ECRHS I and ECRHS II have been published elsewhere.10,11 In ECRHS I 1500 men and 1500 women aged 20 to 44 years

Support was as follows: Australia (Melbourne): Allen and Hanbury’s and the National Health and Medical Research Council. Belgium (Antwerp City and Antwerp South): the Belgian Science Policy Office, National Fund for Scientific Research (G.0402.00), University of Antwerp, Flemish Health Ministry, and Research Foundation of Flanders (G.0.410.08.N.10). Estonia (Tartu): the Estonian Science Foundation (nos. 1088 4350) and Estonian Ministry of Education (SF0180060b09). France: Ministère de la Santé, Glaxo France, Institut Pneumologique d’Aquitaine, Comité de Plan Etat-Région Languedoc-Roussillon, CNMATS, CMRT (90MR/10, 91AI/6), Ministre Delegué de la Santé, RNSP, GSF, and Programme Hospitalier de Recherche Clinique National 2010, France (Bordeaux): Institut Pneumologique d’Aquitaine and INSERM U897—Université Bordeaux Segalen, France (Grenoble): Direction de la Recherche Clinique de Grenoble 2000 (no. 2610), Ministère de l’Équipement et de la Solidarité, Direction Générale de la Santé, CHU Grenoble, Comite des Maladies Respiratoires de l’Isère, and Comité Scientifique AGIRAdom 2011, France (Montpellier): Aventis and Direction Régionale des Affaires Sanitaires et Sociales Languedoc-Roussillon. France (Paris): Ministère de l’Équipement et de la Solidarité, Direction Générale de la Santé, Union Chimique Belge-Pharma, Aventis, Glaxo France, Agence Nationale de la Santé, Région Ile de France, and Domaine d’intérêt majeur. Germany: Bundesminister für Forschung und Technologie. Germany (Erfurt): DFG—German Research Foundation (FR1526/1-1, HE 3294/10-1). Germany (Hamburg): DFG—German Research Foundation (MA 7114/1-NO, 26227/1). Iceland (Reykjavik): Icelandic Research Council, Icelandic University Hospital Hospital, Landspítali University Hospital Research Fund, University of Iceland Research Fund, ResMed Foundation (California), Orkneysta Reykjavík (geothermal plant), and Vegagerðar (Icelandic Road Administration [ICERA]). Italy: Ministero dell’Universita e della Ricerca Scientifica e Tecnologica, CNR, Regione Veneto (RF381/05.93), National Board of Health, and CHIESI. Italy (Pavia): GlaxoSmithKline Italy and Local University Funding for Research, 1998 and 1999. Italy (Turin): Azienda Sanitaria Locale 4 Regioni Piemonte, Azienda OspedalieroCentro Traumatologico OspedalieroCentro Traumatologico Ortopedico—Istituto Clinico Ortopedico Regina Maria Adelaide Regione Piemonte, Department of Public Health and Pediatrics; University of Turin, Unit of Respiratory Medicine, National Health Service, ASL TO2. Italy (Verona): Glaxo Wellcome Spa, Fondazione Cariverona, and Education Ministry (MIUR); Norway (Bergen): Norwegian Research Council (no. 101422/310, no. 214123), Norwegian Asthma and Allergy Association, Glaxo Wellcome AS, Norway Research Council, Western Norway Regional Health Authorities (no. 91.1631), and the Bergen Medical Research Foundation. Spain: Ministerio de Sanidad y Consumo FIS (no. 91/001600/00E-05E, no. 93/0393, no. 97/0035-01, no. 99/0034-01, no. 99/0034-02). Spain (Albacete): Hospital General de Albacete; Hospital Universitario de Albacete, Consejería de Sanidad, and FIS (PS00/02457). Spain (Barcelona): Sociedad Española de Neumología y Cirugía Torácica, Public Health Service (R01 HL62633-01), Consell Interdepartamental de Recerca i Innova-caci Tecnológica (no. 1995SOR-0024), Instituto de Salud Carlos III, Red de Centros de Epidemiología y Salud Pública (C03099), Red de Bases moleculares y fisiológicas de las Enfermedades Respiratorias (C03/011), Red de Grupo Incubación y Medio Ambiente (G03/176), and FIS (PS09/00716). Spain (Galdakao): Basque Health Department and FIS (no. 090151). Spain (Huelva): Hospital General Juan Ramón Jiménez, FIS (PS09/02185), and Servicio Andaluz de Salud. Spain (Or Fired): Consejería de Sanidad Principado de Asturias, FIS (PS00/03310). Sweden (Göteborg, Umeå, and Uppsala): the Swedish Medical Research Council, Swedish Heart-Lung Foundation, Swedish Association against Asthma and Allergy, Swedish Cancer and Allergy Foundation, and Swedish Council for Working Life and Social Research.

Sweden (Umeå): Also received funding from a Vattanbotten County Council ALF grant. Switzerland (Basel): the Swiss National Science Foundation (no. 33CS3/1484701, no. 33CSO1342761, no. 33CSO138796, no. 324730/135673, no. 3247BO140283, no. 3247BO140288, no. 3247BO104284, no. 3247BO104286, no. 3100-059302, no. 3200-052720, no. 3200-042532, no. 4026-082099, PMPD3-P129011, PMPD3P141671/1); the Federal Office for the Environment; the Federal Office of Public Health; the Federal Office of Roads and Transport; and the canton’s government of Aargau, Basel-Stadt, Basel-Land, Geneva, Luzern, Ticino, Valais, and Zürich; the Swiss Lung League; the canton’s Lung League of Basel Stadt/Land-Schaf-te, Geneva, Ticino, Valais, Graubünden, and Zürich; Stiftung ehemals Bündner Heilstätten; SUVA; Freiwillige Akademische Gesellschaft; UBS Wealth Foundation; Talecris Biotherapeutics GmbH; Abbott Diagnostics; the European Commission (no. 018996-GABRIEL); and the Wellcome Trust (WT084703MA). United Kingdom: Asthma UK (formerly known as National Asthma Campaign), Department of Health, South Thames Regional Health Authority, and the Medical Research Council (G0901214/1). The coordination of the European Community Respiratory Health Survey (ECRHS) I and ECRHS II was supported by the European Commission. The coordination of ECRHS III was supported by the Medical Research Council (G0901214/1).

Disclosure of potential conflict of interest: A. F. S. Amaral receives research funding from the Medical Research Council. M. J. Abramson receives research support from E.H. Walters & M.Abramson, Pfizer, and Boehringer Ingelheim and receives consulting fees from AstraZeneca and travel support from Boehringer Ingelheim and Pfizer. P. Demoly receives consulting fees from ALK-Abelló, Circassia, Stallergenes, Allergopharma, Chiesi, Thermo Fisher Scientific, Medam Menarini, AstraZeneca, Pierre Fabre Medicament, and DBV. R. Jögi receives research support from the Estonian Research Council and receives consulting and lecture fees from Boehringer, Novartis, and GlaxoSmithKline and travel support from GlaxoSmithKline and Boehringer. C. Neukirch receives consulting fees and travel support from ALK-Abelló and Stallergenes. D. Nowak receives speaker fees from Mundipharma. I. Pan receives lecture fees from Novartis and MSD and travel support from GlaxoSmithKline, TEVA, and Novartis. R. van Ree receives consulting fees from HAL Allergy BV and speaker fees from Thermo Fisher Scientific. J.-F. Zock receives research support from FIS, Health Institute Carlos III, and the Spanish Ministry of Health. P. G. J. Burney serves on the Novartis Advisory Board. D. L. Jarvis receives research support from the Medical Research Council. The rest of the authors declare that they have no relevant conflicts of interest.

Received for publication April 10, 2015; Revised August 21, 2015; Accepted for publication September 30, 2015.

Available online November 14, 2015.

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were randomly recruited from community-based sampling frames in each center. After completing a short postal screening questionnaire, a random sample of responders was selected to complete an interviewer-led questionnaire and provided a blood sample (1991-1993). In the majority of centers, an additional sample of patients with symptoms highly suggestive of asthma were recruited for the study, but these participants are not included in the present analysis.

In ECRHS II (1998-2002) participants who had completed the extended questionnaire in ECRHS I were reinvistigated and again provided a blood sample. In ECRHS III those who took part in the clinical stages of ECRHS I and II were again contacted, with responders invited to a local testing center where blood samples were taken once more (2008-2013).

Eleven countries are represented in this report: Iceland (Reykjavik), Norway (Bergen), Sweden (Gothenburg, Umeå, and Uppsala), Estonia (Tartu), Belgium (Antwerp South and Antwerp City), Germany (Hamburg and Erfurt), the United Kingdom (Ipswich and Norwich), France (Bordeaux, Grenoble, Montpelier, and Paris), Spain (Barcelona, Galdakao, Albacete, Oviedo, and Huelva), Italy (Pavia, Turin, and Verona), and Australia (Melbourne). Ethical approval for the study from local research ethics committees and written consent from participants were obtained.

Measurement of IgE levels
In all 3 surveys blood samples were obtained and processed under similar conditions. After clotting and centrifuging, serum was stored at −20°C until analysis in a single central laboratory (Pharmacia Uppsala in 1992, Kings College London in 2002, and AMC Amsterdam in 2013/2014) by using the Phadia ImmunoCAP system (now Thermo Fisher Scientific, Uppsala, Sweden).

To assess the effects of potential laboratory bias on the prevalence of IgE sensitization and the mean of total IgE estimates, we conducted duplicate assays on 794 samples (tested at ECRHS I, stored, and tested at ECRHS II) and 475 samples (tested at ECRHS II, stored, and tested at ECRHS III; see Table E1 in this article’s Online Repository at www.jacionline.org). The methods for this correction are described in detail in the Methods section in this article’s Online Repository at www.jacionline.org.

Outcomes
Participants were considered sensitized if allergen-specific IgE to Dermatophagoides pteronyssinus (house dust mite), Felis silvestris catus (cat), and Phleum pratense (Timothy grass) was present in concentrations of greater than 0.35 kU/L. A higher threshold (>0.70 kU/L) was also considered. Atopy was defined as being sensitized to 1 of either house dust mite, grass, or cat. Total IgE, expressed in kilounits/liters, was log-transformed, was kept in log-transformed form and called as continuous outcome for estimation of geometric means (GMs) and their ratios.

Statistical methods
Statistical analyses were performed with Stata software (version 13; StataCorp LP, College Station, Texas). Analyses were restricted to the 3206 participants with information on serum specific IgE and total IgE levels in all 3 ECRHSs (Fig 1). Inverse sampling probability weights were used to standardize the estimation from this population with data on IgE assays from all 3 ECRHSs to the original target population of participants with data on serum specific IgE and total IgE levels in all 3 ECRHSs (see the Methods section in this article’s Online Repository for details on the inverse sampling probability weighted estimation).

The prevalence of sensitization at each survey was determined by using logistic regression with Huber variances considering participants as the clusters. CIs for prevalences and their differences (net change) between ECRHS II and I, ECRHS III and II, and ECRHS III and I were estimated by using the normalizing hyperbolic arc tangent transformation.11 Similarly, by using linear regression, we calculated GM ratios of total IgE levels between ECRHS II and I, ECRHS III and II, and ECRHS III and I. Statistical analyses for each outcome were performed in 2 ways by using uncorrected models and models corrected for potential laboratory bias. Only results of the corrected models are presented in this report. Because data came from multiple centers, we tested for between-center heterogeneity in the uncorrected results by using the methods of Cochran.13

In a final step analyses were repeated as follows: (1) stratified by sex; (2) restricted to lifetime nonsmokers; and (c) stratified by year-of-birth cohort. For this latter step, year-of-birth cohorts were defined by date of birth (1964-1973, 1954-1963, and 1944-1953). The ages of these participants at January 1, 1992 (the approximate midpoint of ECRHS I data collection), would have been as follows: 18 years ≤ age < 28 years, 28 years ≤ age < 38 years, and 38 years ≤ age ≤ 48 years, respectively. Participants from Tartu, Estonia, were recruited at age 20-44 years in 1994 and would have been less than 20 years old on January 1, 1992; hence 18 years is the lower age limit. Members of each age cohort would have been 10 years older on January 1, 2002 (during the ECRHS II data collection), and 20 years older on January 1, 2012 (during the ECRHS III data collection). This approach allowed comparison of earlier cohorts with later cohorts at approximately the same ages.

RESULTS
A total of 3,206 (30.6%) of the 10,478 participants who provided a blood sample in the first survey took part and again provided a sample in both ECRHS II and III. The median age of participants in ECRHS I was 34.9 years (interquartile range, 28.6-40.5 years), half were males, and forty-five percent were lifetime nonsmokers. There was variation between centers in the proportion of participants who provided samples at ECRHS I and then went on to provide samples at ECRHS II and ECRHS III (minimum, 13.6% in Pavia; maximum, 58.6% in Reykjavik). Factors associated with response were older age and being a nonsmoker. Response was not associated with sensitization at baseline, sex, and reporting of wheeze (see Table E2 in this article’s Online Repository at www.jacionline.org), although those who took part in all 3 surveys reported waking with breathlessness less frequently.

Net change in IgE sensitization and total IgE levels
Laboratory-corrected net changes in the prevalence of IgE sensitization to each of the allergens and in GMs of total IgE levels were calculated by using the methods of Cochran. Results are presented in Table E3 in this article’s Online Repository at www.jacionline.org.
levels over a period of 20 years are shown in Table I. Between ECRHS I and ECRHS II, there was no significant change in the prevalence of IgE sensitization to any of the allergens by using either the low or high cutoff levels.

Over the 20 years of follow-up (ie, between ECRHS I and ECRHS III), the prevalence of IgE sensitization to house dust mite, cat, and at least 1 allergen decreased. By using the 0.35 kUA/L cutoff, the prevalence of sensitization to grass remained stable, but when the 0.70 kUA/L cutoff was used, there was evidence of a reduction in sensitization. These changes were similar in men and women (see Table E3 in this article’s Online Repository at www.jacionline.org).

For some estimates, there was evidence of heterogeneity between countries, but no clear pattern in this variation was observed by latitude (Fig 2), response rate (see Fig E1 in this article’s Online Repository at www.jacionline.org), or prevalence of sensitization at baseline (see Fig E2 in this article’s Online Repository at www.jacionline.org).

Overall, there was a significant decrease in total IgE levels over the 20 years of follow-up (GM ratio, 0.63; 95% CI, 0.58-0.68). This generalized decrease in total IgE levels occurred in all centers, although the magnitude of the change varied (heterogeneity between centers, P < .001; see Fig E3 in this article’s Online Repository at www.jacionline.org). Patterns were similar in men and women (see Table E3).

Restriction of analyses to the 1304 participants who were lifetime nonsmokers did not materially alter the results reported above (see Table E4 in this article’s Online Repository at www.jacionline.org).

Association of net change with age and cohort

In ECRHS I the prevalence of IgE sensitization to house dust mite, cat, and at least 1 allergen was higher in younger adults (ie, those born more recently) than in older adults (Table II).

Over the 20-year period, the prevalence of sensitization to house dust mite decreased in all age groups to a similar extent, and there was little evidence that the age-specific prevalence of sensitization to house dust mite was different between those born more recently and those born earlier (Fig 3, A). Overall, the picture was one of a decrease in sensitization with age, with decreases occurring throughout adult life. This was broadly similar for sensitization to cat (Fig 3, C). However, these patterns were different for sensitization to grass. Although there was evidence of a decrease in sensitization to grass in those who were the oldest at recruitment (ie, the earlier cohort), decreases were not seen in those who were born more recently. As a result, there were marked differences in the age-specific prevalence of sensitization to grass between cohorts with higher age-specific prevalence in those born after 1964 (Fig 3, B). The prevalence of IgE sensitization to at least 1 of house dust mite, grass, and cat showed a pattern similar to that of sensitization to house dust mite and cat. The most recent cohort had the highest prevalence at younger ages, but these cohort-related differences were not apparent in later adult life (Fig 3, D). Similar patterns were observed when using the cutoff of 0.70 kUA/L (see Table E5 in this article’s Online Repository at www.jacionline.org).

The population GM of total IgE was lower at each follow-up in all cohorts over the 20-year period of follow-up, and the more recent cohorts had lower total IgE levels than those born earlier at the equivalent ages (Fig 4 and Table II).

DISCUSSION

We have shown that the prevalence of sensitization to at least 1 of house dust mite, cat, or grass has decreased within a large population-based adult cohort followed over a period of 20 years. There was a decrease in the prevalence of sensitization to house dust mite and cat, and the GM total IgE levels also decreased. Sensitization to grass did not follow these patterns so clearly, showing instead an increase at younger ages and aging effects only at older ages.

The strengths of this study are the population-based nature of the sample derived from several parts of Europe and Australia, the prolonged period of follow-up, and the standardized handling and
testing of samples between centers and over time. Changes in laboratory staff, consumables, and methods between surveys could lead to bias in prevalence estimates, and to address this, we have used information from duplicate assays of hundreds of samples to adjust our estimates. As with all cohorts, there has been attrition during the 20-year period of follow-up, and the analyses we present are based on participants who have taken part in all 3 phases of the study. We are aware that considerable loss to
follow-up has the potential to induce bias, and therefore to account for small differences between these subjects and the initial cohort at baseline and to enhance the external validity of our results, we have corrected our models with inverse sampling probability weights. This method generates estimates that apply to the population we sampled at baseline. We are unable to say whether the start of the age-related decrease in sensitization occurs around the age of 20 years or earlier because the ECRHS is a cohort of adults only.

To date, few other population-based studies have reported on longitudinal changes in sensitization by measuring serum specific IgE levels. These earlier reports, both from Denmark, are of smaller samples and mostly over shorter time periods. Linneberg et al studied changes over an 8-year period in serum specific IgE levels to at least 1 of 6 allergens in about 400 adolescents and adults in Copenhagen, reporting an increase in the prevalence of IgE sensitization, especially among those born in the 1960s or later. Older adults (>40 years, n = 695) living in the same

TABLE II. Net change in IgE sensitization (>0.35 kUA/L) to house dust mite, grass, and cat and total IgE levels (kilounits per liter) over 20 years by year-of-birth cohort

<table>
<thead>
<tr>
<th></th>
<th>1964-1973 (n = 736)</th>
<th>1954-1963 (n = 1314)</th>
<th>1944-1953 (n = 1156)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ECRHS I</td>
<td>ECRHS II vs I</td>
<td>ECRHS III vs I</td>
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<tr>
<td></td>
<td>ECRHS I</td>
<td>ECRHS II vs I</td>
<td>ECRHS III vs I</td>
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<td></td>
<td>ECRHS I</td>
<td>ECRHS II vs I</td>
<td>ECRHS III vs I</td>
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<td></td>
<td>ECRHS I</td>
<td>ECRHS II vs I</td>
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<tr>
<td></td>
<td>ECRHS I</td>
<td>ECRHS II vs I</td>
<td>ECRHS III vs I</td>
</tr>
<tr>
<td>House dust mite</td>
<td>18.6</td>
<td>−0.6 (−3.0 to 1.8)</td>
<td>−4.1 (−6.7 to −1.5)</td>
</tr>
<tr>
<td>Grass</td>
<td>20.6</td>
<td>3.3 (0.4 to 6.2)</td>
<td>1.5 (−1.8 to 4.9)</td>
</tr>
<tr>
<td>Cat</td>
<td>10.5</td>
<td>0.2 (−2.2 to 2.6)</td>
<td>−0.7 (−3.5 to 2.0)</td>
</tr>
<tr>
<td>House dust mite, grass, or cat</td>
<td>33.5</td>
<td>1.9 (−1.3 to 5.1)</td>
<td>−2.1 (−6.1 to −1.3)</td>
</tr>
<tr>
<td>Total IgE</td>
<td>29.9</td>
<td>0.81 (0.72 to 0.91)</td>
<td>0.61 (0.54 to 0.68)</td>
</tr>
</tbody>
</table>

FIG 3. Prevalence of IgE sensitization to house dust mite (A), grass (B), cat (C), and at least 1 of these 3 allergens (D) over 20 years of follow-up by year-of-birth cohort.
city and followed for 20 years showed no change in sensitization over a 20-year period in prevalence of IgE sensitization to at least 1 of 19 allergens. Other studies looked at changes in sensitization by performing skin prick tests and reported increases with aging. However, skin prick tests are much more difficult to standardize over different periods because they are prone to fieldworker variation, with changes in skin prick test reagents being difficult to assess.

Barbee et al studied 1100 participants in the United States and reported a decrease in total IgE levels with age in children and young adults but not in older adults. In ECRHS total IgE levels decreased with aging within each cohort, with more recent cohorts having lower total IgE levels than earlier ones at the same age. In a previous report we showed that smoking associated differently with sensitization to different aeroallergens and in a dose-response manner with total IgE levels. Therefore we hypothesized that changes in sensitization over time could be related to decreasing smoking rates and that lifetime nonsmokers would not show changes in sensitization. Our present findings show that a decrease in sensitization is unlikely to be related to smoking cessation. The decrease in total IgE levels in our study might in part be explained by a decrease in helminth infestation, as observed by others in children. We saw no evidence of change in the prevalence of IgE sensitization to house dust mite, cat, and grass, and at least 1 of these 3 as the cohort aged over the initial 10 years of follow-up of the ECRHS. This observation is confirmed within this second report, but we go on to show that prevalence does decrease over 20 years and appears greater when subjects are aged about 40 years or older. This finding might be explained by immunosenescence, which seems to be more evident after 50 years of age and corresponds to age-related changes in the number and function of cells from the immune system. The production of IgE, which is dependent on an interaction between B and T cells, might decrease as a consequence of the naturally occurring involution of the thymus; the thymic output of T cells per day in a 50-year-old is about 33% lower than that in a 25-year-old. Our findings are supported by animal studies, which suggest that the production of IgE to an allergen challenge is higher in younger than older animals. In one of these studies, the transplantation of thymocytes into young (8 weeks old) mice resulted in no change in IgE response, whereas that into aged (65 weeks old) mice resulted in an enhanced IgE response similar to that into young mice.

One might expect all markers of atopy to follow similar age/period/cohort patterns. Our report suggests house dust mite and cat might be different to grass, but we can only speculate as to the reason for this. One explanation for the decrease in sensitization to house dust mite and cat could be avoidance by the participants. We cannot assess whether participants avoided house dust mite allergen, but we do know that the prevalence of cat ownership among those with IgE at all 3 time points has not decreased over the 20 years of follow-up (16.9% at ECRHS I and 19.5% at ECRHS III). This supports the hypothesis that the decrease in prevalence of sensitization to cat is more likely due to aging-related immunosenescence. There are differences in the epidemiology of sensitization to each of the 3 allergens, particularly with respect to factors associated with the hygiene hypothesis. Larger sibships protect younger siblings from hay fever and sensitization to grass more strongly than from asthma and sensitization to house dust mites. Decreasing family size over the last decades might explain the less marked aging effect for grass than for other allergens. Changes in the level of exposure to pollens might have had a role in our findings. There are also reports suggesting that pollens in our more modern society are more allergenic than they have been previously, which could be related to the high levels of air pollutants, such as ozone, nitrogen dioxide, and carbon dioxide. The presence of unmeasured factors might also have a role in the different patterns observed in sensitization to the 3 allergens.

In summary, over a period of 20 years, the prevalence of specific IgE sensitization to house dust mite and cat, but not grass, significantly decreased in the multinational cohort of adults from the ECRHS as a consequence of aging, being more evident among those aged 40 years or older.

We thank the participants, field workers, and data managers of this study for their time and cooperation.

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**Key messages**

- Allergen-specific and total IgE levels decrease after the age of 20 years as subjects become older.
- Kinetics of IgE sensitization decrease differently for different allergens and might be faster after 40 years of age.
- The biological mechanism and environmental determinants for IgE sensitization that decrease with aging need to be explored so that we can improve our understanding of the cause of atopy and atopic diseases.

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