Resolved allergen-specific IgE sensitization among females and early poly-sensitization among males impact IgE sensitization up to age 24 years

To the Editor:
Up to half of the adult population has allergen-specific immunoglobulin E antibodies (sIgE). Even though females and males are not equally affected, relatively little is known regarding mechanisms behind differences in IgE sensitization between females and males. IgE poly-sensitization has been defined as IgE reactivity to several nonrelated (or not obviously related) allergenic source materials and has been shown to increase with age and correlate with disease expression and multimorbidity. Although females and males do not seem to differ regarding IgE poly-sensitization in adulthood, a recent study indicates that IgE poly-sensitization is more common among boys than girls in childhood. Interestingly, findings from the longitudinal Isle of Wight study indicate that more females than males tend to outgrow their IgE sensitization. Investigation of the nature history of IgE sensitization requires large longitudinal population-based studies including repeated measurements of sIgE. We therefore undertook a study to explore the dynamics of IgE sensitization from early childhood to young adulthood in relation to sex, including new and resolved IgE sensitization, poly-sensitization as well as IgE trajectories over time.

We therefore undertook a study to explore the dynamics of IgE sensitization from early childhood to young adulthood in relation to sex, including new and resolved IgE sensitization, poly-sensitization as well as IgE trajectories over time. In the Swedish population-based birth cohort BAMSE (N = 4089), participants have been followed up to young adulthood including collection of blood at ages 4, 8, 16 and 24 years for analysis of specific IgE to 14 common food (peanut, soy, wheat, milk, egg, cod) and airborne (timothy, birch, mugwort, cat, dog, horse, house dust mites and Cladosporium herbarum) allergens. Females (n = 656) and males (n = 570) with complete data on sIgE at all four follow-ups were included for the current study. Any IgE sensitization was defined as sIgE ≥ 0.35 kUA/L to one or more of the tested foods and/or airborne allergens. Poly-sensitization was defined as sIgE ≥ 0.35 kUA/L to four or more specific allergens at the same follow-up, as in previous reports from BAMSE. New IgE sensitization: any IgE sensitization at a follow-up in an individual with no sIgE sensitization at the previous follow-up. Resolved IgE sensitization: no IgE sensitization to any of the specific allergens at a follow-up in an individual that displayed any IgE sensitization at the previous follow-up.

The study was approved by the regional ethics committee in Stockholm, ethics approval number: 2016/1380-31/2, and participants and/or caregivers provided written informed consent. Details on data collection and definitions are presented in the Methods section in this article’s supporting information.

A similar proportion of females (22.6%) and males (23.7%) were IgE-sensitized to any of the 14 allergens at 4 years, Figure 1. With increasing age, the prevalence of any IgE sensitization increased for both sexes, but a steeper increase was seen for males. Figure 1 also shows how many allergens females and males were sensitized to at the different ages. Fewer IgE-sensitized females than males were poly-sensitized to four or more allergens at all ages with the most pronounced difference at age four years, 12.6% (20/148) vs. 31.1% (42/135). The corresponding rates at 8 years were 30.7% (65/212) vs. 42.9% (85/198). Differences diminished further with age, and at 16 and 24 years, differences were small. Very few poly-sensitized individuals outgrew their sensitization between follow-ups, zero individuals between 4 and 8 years, one between 8 and 16 years and five between 16 and 24 years. Thus, in total four females and two males with poly-sensitization outgrew their IgE sensitization over time.

We further explored IgE poly-sensitization in relation to sex over time using generalized estimating equations, and the same analysis was used to explore new and resolved IgE sensitization, Figure 2. Covariates included in Table S2 were tested as potential confounders using backward selection, but none of the factors impacted the associations between sex and any of the outcomes, and therefore, unadjusted analysis is presented. Male sex was significantly associated with IgE poly-sensitization at 4 years (OR: 2.75, 95% CI: 1.41–5.37) but not at other ages, Figure 2. Sex was not associated with new IgE sensitization at the ages 4 and 8 years. However, at ages 16 and 24 years more males than females developed new IgE sensitization. The overall OR for the impact of male sex for new IgE sensitization was 1.15, 95% CI: 0.97–1.33. In contrast, resolved IgE sensitization was less common among males than females at all ages, overall OR: 0.37, 95% CI: 0.25–0.53. Resolved IgE sensitization was seen both for food and airborne allergens with comparable sex differences (data not shown).

Both new and resolved IgE sensitization was characterized by significantly lower levels of specific IgE at all ages, while IgE poly-sensitization was associated with significantly higher levels of specific IgE at all ages (data not shown).
The current study includes only 30% of the original cohort. To facilitate evaluation of generalizability, we present baseline characteristics, allergic diseases and any IgE sensitization at ages 4, 8 and 16 years for the 1226 individuals and for the original cohort, Table S1. As shown in Table S1, there were some differences in basic characteristics. Also, allergic diseases and IgE sensitization tended to be more prevalent, especially at higher ages, in the group that provided blood at all follow-ups, even though differences were small.

A higher proportion of females (656/2024, 32.4%) than males (570/2064, 27.6%) provided blood at all 4 follow-ups and were included in the current study. To evaluate whether selection bias might impact the sex differences found in our study, we compared background factors between included females and males. Differences were small, Table S2. In accordance with the data in Table S1, any IgE sensitization tended to be more prevalent both among included females and males. However, differences were not more pronounced among males (data not shown).

In this longitudinal population-based study, we show that a comparable number of females (22.6%) and males (23.7%) display any IgE sensitization at 4 years. With age, IgE sensitization became increasingly more common among both females and males. The increase was steeper among males with 52.6% of males displaying any IgE sensitization at age 24 years compared to 38.7% of females. We found that differences in trajectories of IgE sensitization from...
childhood to young adulthood between females and males can largely be explained by resolved IgE sensitization among females and early IgE poly-sensitization among males. The finding that females outgrow their IgE sensitization to a higher degree than males confirms previous results from the Isle of Wight study in which females tended to be more likely to outgrow their sensitization than males.\(^6\)

Poly-sensitized individuals were unlikely to outgrow their sensitization. Thus, the accumulating sex differences in overall sensitization seen with increasing age (Figure 1) are probably partly explained by the high degree of early poly-sensitization among boys. Our results are in accordance with data from a cross-sectional population-based Polish study including 1409 individuals aged 6 to 44 years.\(^5\) They found polyvalent sensitization (defined as sIgE to two or more allergens) to be significantly more prevalent among 6-7 year old boys compared to girls the same age while there were no significant differences in the older age groups.\(^5\) Results from the German Multi-Centre Allergy Study birth cohort indicate that the earlier the sensitization onset, the stronger the tendency for poly-sensitization.\(^7\) Thus, even though a similar proportion of females and males displayed IgE sensitization at 4 years it is possible that males developed their sensitization at a younger age compared to females (i.e. below age 4).

The genetic influence on poly-sensitization has only been evaluated in a limited number of studies and suggests associations with the HLA and C11orf30-LRRC32 regions, as well as Th2 signalling genes.\(^3\) Sex-specific genetic effects on sensitization and allergic diseases have been reported in the literature,\(^10\) but no consistent picture or explanation of the underlying biology has emerged. Whether there are primarily genetic, hormonal or environmental factors associated with the observed sex differences in IgE sensitization trajectories in our study, resolved sensitization in females and poly-sensitization in males, remain to be further investigated.

Strengths of our study include the population-based design, long follow-up time and that blood was collected for analyses of sIgE at four time points. Adjustment for several potential confounders did not affect the results, although residual confounding effects can never be ruled out in an observational study. A limitation is that only 30% of the original cohort were included and rates of sensitization are probably higher compared to the general population, which may affect the generalizability of the findings. We explored three outcomes, and if the Bonferroni method had been applied, a p-value of .017 would be significant. The associations for sex and IgE poly-sensitization at 4 years as well as all associations regarding sex and resolved IgE sensitization are significant at that level. At the same level, the association for sex and new IgE sensitization was significant at 16 years but not at 24 years. A weakness of our study is that IgE sensitization was not measured before age 4 years.

In summary, sex impacts IgE trajectories from childhood to young adulthood. We identified two factors that contribute to these sex differences: resolution of allergen-specific sensitization in females and higher rates of allergen poly-sensitization in males. Further analyses of the underlying determinants for these immunological events are warranted.

ACKNOWLEDGMENTS

We thank the children and parents participating in the BAMSE cohort and all staff involved in the study through the years. We would also like to thank Professor Magnus Wickman, former PI of the BAMSE study, for valuable input.

FUNDING INFORMATION

This study was supported by grants from the European Research Council (TRIBAL, grant agreement 757919), the Swedish Research Council, the Åke Wiberg foundation, Kronprinsessan Lovisas research foundation, the Swedish Heart-Lung Foundation, Region Stockholm (ALF project, and for cohort and database maintenance), The Konsul Th C Bergh’s Foundation, The Swedish Society of Medicine, The Pediatric Research Foundation at Astrid Lindgren Children’s Hospital, The Sven Jerring Foundation, The Magnus Bergwall foundation, The Hesselman Foundation, The Swedish Asthma and Allergy Association’s Research Foundation, The Swedish Cancer and Allergy Foundation, The King Gustaf V 80th Birthday Foundation. Thermo Fisher Scientific kindly provided reagents for IgE analyses.

CONFLICT OF INTEREST

EM has received lecture fees from Novartis, Sanofi and Thermo Fisher Scientific outside the submitted work. NB has received consultancy fees from Pfizer and Sanofi outside the submitted work. MvH has received lecture fees from Thermo Fisher Scientific and ALK; and consultancy fees from Biomay AG, Vienna, Austria and Hycor Biomedical LLC, CA, US, outside the submitted work. Dr. Westman reports personal fees from ALK (consultancy fees), outside the submitted work. The other authors report no conflict of interest relevant to this article.

AUTHORS CONTRIBUTIONS

Data collection was managed by EM, IK and AB. Statistical analysis was conducted by NB and EM. Analysis and drafting of the manuscript were conducted by NB and EM. All authors participated in critical revision of the manuscript, provided important intellectual input and approved the final version.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.
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SUPPORTING INFORMATION
Additional supporting information may be found online in the Supporting Information section.

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