Prevalence and early-life risk factors for tree nut sensitization and allergy in young adults

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Abstract

Background: Tree nut allergy may cause anaphylaxis. There are limited population-based studies on prevalence and early-life risk factors.

Methods: We evaluated the prevalence of reported symptoms and allergic sensitization to tree nuts at age 24 years in the BAMSE population-based cohort study and assessed early-life factors associated with the development of tree nut allergy.

We estimated tree nut allergy prevalence, by analysing questionnaire data on tree nut ingestion and symptoms at age 12, 16 and 24 years, and IgE sensitization at age 24 years to hazelnut, walnut, pecan, cashew, pistachio, Brazil nut, almond extracts and allergen molecules Cor a 1, 9, 14 (hazelnut), Jug r 1 (walnut) and Ana o 3 (cashew).

We evaluated eczema, asthma, food allergies, inherited risk of allergy and gender as potential early-life risk factors.

Results: Data were available for 2215/4089 (54%) BAMSE study participants, for estimation of the prevalence of tree nut sensitization (21.2%), tree nut allergy symptoms (9.8%) and combined sensitization and symptoms (7.9%, 2.1% for storage protein sensitization and symptoms, 4.3% for any sensitization and non-mild symptoms). Sixty-three per cent of sensitized individuals (295/470) were asymptomatic, but only 76/470...
Peanuts and tree nuts account for 70–90% of all food related deaths by anaphylaxis, where of tree nuts stands for 18–40%. Ingestion of tree nuts by mistake is common as it is a frequent ingredient in many processed foods. Since allergic reactions to nuts can be severe and allergy to peanuts and tree nuts tend to last for the entire life of the affected individuals, they constitute a large health concern.

The reported prevalence of tree nut allergy varies across regions and depends on whether the allergy is self-reported or confirmed diagnostically. A systematic review of studies across the world estimated the worldwide prevalence of probable tree nut allergy to range from 0.05% to 4.9%. Prevalence estimates of reactions to tree nuts including oral allergy syndrome were 8.0 – 11.4%.

Conclusions: In this Swedish cohort, we found tree nut whole extract sensitization is common but usually asymptomatic. Storage protein sensitization is a more reliable indicator of tree nut symptoms. Tree nut allergy is associated with early onset, persistent and severe atopic disease.

KEYWORDS
Ana o 3, BAMSE, birth cohort, Cor a 1, Cor a 14, Cor a 9, Jug r 1, molecular allergology, sensitization, tree nut allergy

GRAPHICAL ABSTRACT

2215 individuals from the BAMSE-cohort with questionnaire data on tree nut symptom at 12, 16 and 24 years and data on IgE reactivity against hazelnut, walnut, pecan, cashew, pistachio, brazil nut, almond and against the allergen molecules Cor a1, 9, 14 (hazelnut), Jug r 1 (walnut) and Ana o 3 (cashew) were analysed. Most tree nut extract sensitized individuals were asymptomatic at 24 years of age. Early atopic manifestations were associated with later tree nut storage protein sensitization and symptoms.

Key messages
• In this Swedish cohort, tree nut extract sensitization was common in adulthood, but usually asymptomatic.
• IgE to tree nut storage proteins predicted tree nut symptoms better than tree nut extract.
• Early eczema, asthma and egg allergy were associated with developing tree nut allergy by adulthood.

A double-blind, placebo-controlled oral food challenge is the gold standard for diagnosing food allergy. However, this procedure, where an oral intake of the food is performed in a clinical setting, can potentially pose a high-risk, is time-consuming and uncomfortable for the patient. Therefore, many food allergy diagnoses are the
results of allergen specific sIgE-antibody (sIgE-ab) tests combined with clinical history.

Molecular allergy diagnostics have made it possible to better predict whether a reaction to a food will be local oral symptoms, referred to as OAS or more clinically relevant systemic symptoms. In birch pollen allergy, a cross-reaction between the birch pollen allergen Bet v 1 and the hazelnut allergen Cor a 1 can cause light oral symptoms related to intake of hazelnuts. In the clinically most relevant tree nut allergens are storage proteins, resistant to both heating and gastrointestinal digestion. In hazelnut, the storage proteins Cor a 9 (11S Globulin) and Cor a 14 (2S Albumin) are the most clinically important allergen molecules. Analyzing sIgE-ab to these proteins increases the diagnostic specificity as they are associated with more severe symptoms. In cashew nut and walnut, sIgE-ab to the 2S Albumins Ana o 3 and Jug r 1, respectively, have been shown to be useful tools for predicting clinically relevant allergy in hospital-based studies.

It has been shown that among children, increasing age is related to increased polysensitization to different nuts. In a previous study, 19% of tree nut-sensitized participants were polysensitized to different nuts at 2 years and 86% at 5-14 years. In the same study, clinical allergy to more than one nut increased from 2% at 2 years to 47% at 14 years.

Tree nut allergy is an understudied area despite its clinical relevance with possibly increasing prevalence and potential to cause anaphylaxis. The relationship between prevalence of sensitization to tree nuts and prevalence of clinical symptoms has only scarcely been investigated in population-based settings. A recent review article of the available literature on tree nut allergy concluded that there are limited region-specific studies based on robust food allergy measures in population cohorts with longitudinal follow-up. Furthermore, there are still uncertainties regarding potential risk factors for tree nut sensitization, especially tree nut storage protein sensitization and whether polysensitization increases the likelihood of clinical tree nut allergy.

The aim of this study was to determine the prevalence of tree nut allergy in young adults from a population-based birth cohort in relation to sensitization at extract and molecular allergen levels, reported symptoms and early-life factors.

2 | MATERIALS AND METHODS

2.1 | The BAMSE project

The Swedish birth cohort BAMSE (Barn/Children Allergy/Allergy Miljö/Milieu Epidemiologi /Epidemiology Stockholm) cohort included 4089 children born 1994-1996 in Stockholm, Sweden, in an unselected population-based setting. Details on study design, enrollment, criteria for inclusion and procedures for data collection have been described elsewhere. Background data were collected at inclusion (median age 2 months). Detailed questionnaires collecting information on allergic diseases and selected lifestyle and environmental exposures were answered by the parents at 1, 2, 4, 8, 12 and 16 years and self-reported at 24 years of age. Clinical examinations including blood samples and lung function tests were performed at 4, 8, 16 and 24 years of age as described previously. The study population is described in Figure S1.

2.2 | Data collection

2.2.1 | Definitions of allergic symptoms

We used data collected from the 12-, 16- and 24-year follow-up questionnaires. Definitions of asthma, eczema and rhinitis have been presented elsewhere. The tree nut symptom questions differed slightly between years 12, 16 and 24 and are listed in online supplement.

2.2.2 | Tree nut symptoms at 24 years of age

Specific symptoms upon exposure to tree nuts (hazelnut, cashew/pistachio, walnut/pecan, almond/other nuts) at 24 years of age or reported avoidance of tree nuts at 24 years of age in combination with reported specific symptoms to tree nuts in at least one of the questionnaires at age 12 or 16 years (see online supplement).

2.2.3 | Oral allergy syndrome

In the 24-year survey, the oral allergy syndrome was equal to the symptom ‘itching/swelling sensation in mouth/throat’. In the 16-year survey, the symptom was ‘itch in mouth, throat, ears’, and at 12 years ‘itch in mouth, throat, eyes’. Reporting only these symptoms were specified to be marked as OAS, not combined with other symptoms.

2.2.4 | Definition of possible associated factors

All early-life factor definitions and disease definitions are specified in online supplement methods section.

2.2.5 | Sensitization

All blood samples collected at 24 years of age were analysed for two mixes of common nuts and peanut: fx1® (peanut, hazelnut, Brazil nut, almond, coconut) and fx22® (pecan nut, cashew nut, pistachio, walnut) with the ImmunoCAP System (Thermo Fisher Scientific, Uppsala, Sweden). Sera that scored positive (IgE >0.35 kU/l) for a mix were further analysed for the individual allergens in the mix. If the sIgE-ab level to hazelnut was ≥0.35 kU/l, sIgE-ab to Cor a 1, Cor a 9 and Cor...
a 14 were analysed, and if the sIgE-ab level to walnut or cashew nut was ≥0.35 kU/l, sIgE-ab to Jug r 1 and Ana o 3 were analysed, respectively. sIgE-ab sensitization to food allergen extracts (fx1® and fx22®) was defined as sIgE-ab ≥0.35 kU/l and to specific allergen molecules (Cor a 1, Cor a 9, Cor a 14, Jug r 1, Ana o 3) sIgE-ab ≥0.1 kU/l.

2.3 | Statistical methods

Prevalence rates were presented as numbers and proportions, mean levels were calculated with addition of all positive values divided by number of positive values and median level was the middle value of the observations listed in size order. For calculation of sensitivity, specificity, PPV and NPV, see online supplement methods. Two-tailed t tests on log transformed values were used to account for group differences in continuous values with skewed distribution, that is the sIgE-ab levels. P-values of <0.05 were considered statistically significant. Odds ratios (OR) with 95% confidence intervals (CIs) were calculated using logistic regression for tree nut sensitization at 24 years in relation to early risk factors such as eczema, asthma, other food allergies, sex and parental allergy. OR estimates with 95% CI were presented from both univariate and multiple logistic regression. Logistic regression was also used for estimation of reported allergy in relation to sIgE-ab levels to the different tree nut allergen molecules. Probability calculations for the likelihood of tree nut symptoms were performed based on the results from the logistic regression. Statistical analyses were conducted using STATA Statistical Software (15.1).

3 | RESULTS

3.1 | Tree nut symptoms and sensitization

Out of the 2,215 participants included in our study, a total of 217 participants either reported clinical symptoms to tree nuts at 24 years of age or avoided tree nuts at 24 years and reported clinical symptoms at 12 or 16 years. Those individuals were considered as tree nut symptomatic in our analyses, including individuals reporting OAS symptoms, see Figure S2. A comparison of individuals participating in the 24-year follow-up and individuals in the original cohort is presented elsewhere.16

We found that the overall prevalence for tree nuts extract sensitization was 21.2%, and 7.9% both had symptoms and were sensitized. If participants with OAS only were excluded, 4.3% both reported symptoms and were sensitized. Sensitization to hazelnut was 20.6% and the most frequently observed sensitization. In total, 7.3% reported clinical symptoms of hazelnut allergy, while 6.1% reported symptoms and were sensitized to hazelnut. Corresponding numbers for the other tree nuts are presented in Table 1. Twenty-five individuals reported tree nut symptoms but denied tree nut avoidance. Of these, 18 were tree nut-sensitized; 17 to hazelnut, two to cashew and pistachio and four to almond. 72% (18/25) reported OAS only. Among the 217 tree nut symptomatic individuals, the most common phenotype was symptoms to all tree nuts (n=55, 25.3%) and the second most common phenotype was symptoms to hazelnut only (n=40, 18.4%), see Table S1. Among the 1,996 participants who did not report any tree nut allergy symptoms, the prevalence of tree nut sensitization was 14.6%. Thus, the majority of tree nut-sensitized individuals in the cohort did not report any tree nut symptoms. We explored differences in sIgE-ab levels to the included tree nuts among sensitized individuals with and without symptoms. sIgE-ab levels were significantly higher for most nut extracts and all allergen molecules among those who reported symptoms (Figure 1A and Figure 1B).

3.2 | Allergen molecules

Sensitization to any of the analysed tree nut storage proteins (ie Cor a 9, Cor a 14, Jug r 1, Ana o 3) was 3.5%. 2.1% were storage protein sensitization and reported symptoms, and prevalence of sensitization to Cor a 1 was 19.3%. Corresponding numbers for the other tree nut proteins are presented in Table 2. The relation between

| TABLE 1 Prevalence of tree nut sensitization and reported clinical symptoms. N=2215 |
|---------------------------------------------------------------|
| Prevalence                              | Sensitized n (%) | Reported symptoms n (%) | Sensitized + reported symptoms n (%) |
|-----------------------------------------|------------------|-------------------------|-------------------------------------|
| Hazelnut                                 | 457 (20.6%)      | 162 (7.3%)              | 134 (6.1%)                          |
| Almond                                   | 168 (7.6%)       | 122 (5.5%)              | 56 (2.5%)                           |
| Cashew and pistachio                     | 96 (4.3%)        | 93 (4.2%)               | 34 (1.5%)                           |
| Walnut and pecan                         | 72 (3.3%)        | 126 (5.7%)              | 30 (1.4%)                           |
| Brazil nut                               | 48 (2.2%)        | n.a.                    | n.a.                                |
| Any tree nut                             | 470 (21.2%)      | 217 (9.8%)              | 175 (7.9%)                          |
| Any tree nut excl. OAS                   | n.a.             | 109 (5.2%)              | 90 (4.3%)                           |

Note: Sensitization to the respective tree nut, at 24 years and reported symptoms at 12/16/24 years. Symptoms from Brazil nut were not asked for in the questionnaire.
Abbreviation: N.a, Not applicable.
sensitization to birch extract, hazelnut extract and the hazelnut specific allergen Cor a 1 is described in Figure 2. Of the participants sensitized to hazelnut extract, 97% were also sensitized to birch pollen extract. Among those sensitized to the hazelnut allergen molecule Cor a 1, 97% were also sensitized to birch pollen extract. Among those sensitized to hazelnut extract, 9% were sensitized to Cor a 14 and 14% to Cor a 9.

**TABLE 2** Prevalence of tree nut allergen molecule sensitization at 24 years. N = 2215

| Allergen Molecule | Prevalence (%) | Median sIgE-ab, kU/L (IQR) |
|-------------------|----------------|---------------------------|
| Cor a 1 (hazelnut) | 19.3%          | 8.1 (2.0–25)              |
| Cor a 9 (hazelnut) | 2.8%           | 0.4 (0.19–2.1)            |
| Cor a 14 (hazelnut)| 1.9%           | 0.35 (0.13–4.1)           |
| Jug r 1 (walnut)  | 1.3%           | 1.9 (0.22–5.6)            |
| Ana o 3 (cashew)  | 1.2%           | 1.0 (0.16–3.6)            |
| Any tree nut storage protein* | 3.5% | n.a. |

Abbreviation: N.a., Not applicable.
*storage protein molecules: Cor a 9, Cor a 14, Jug r 1, Ana o 3.

**FIGURE 2** (A-C) Relationship between sensitization to birch pollen and hazelnut extract and hazelnut allergen molecules. Venn diagrams illustrating overlaps between (A) sensitization to hazelnut extract, birch pollen and Cor a 1, (B) sensitization to hazelnut extract, Cor a 14 and Cor a 9 and (C) sensitization to Cor a 1, Cor a 9 and Cor a 14. N = 2,215

Cor a 1, all but one participant was at the same time sensitized to birch pollen extract. In contrast, among participants sensitized to hazelnut extract, 9% were sensitized to Cor a 14 and 14% to Cor a 9. Evaluation of co-sensitization to the hazelnut allergen molecules Cor
a. Cor a 9 and Cor a 14 among individuals with sensitization to any hazelnut molecule revealed that 83% were sensitized to Cor a 1 only.

We also compared individuals with sensitization to both Cor a 9 and Cor a 14 (n=31) to those sensitized to either Cor a 9 or Cor a 14 (n=41) regarding reported symptoms to hazelnut. Individuals with sensitization to both allergens were more prone to report any hazelnut symptoms; 81% among those with dual sensitization vs 39% among sensitized to either Cor a 9 or Cor a 14 (p<0.01). Significant differences in prevalence of reported symptoms to hazelnut were seen with higher prevalence for swollen face (p<0.01), urticaria (p=0.014) and OAS (p<0.01) in the dual-sensitized group.

For results regarding probability of allergic symptoms in relation to specific IgE-Ab levels and polysensitization and for specificity and sensitivity calculations, see online supplement results section, Figures S3–S5 and Table S4.

### 3.3 | Associated factors of tree nut symptoms and storage protein sensitization

The odds ratios (ORs) for reported tree nut symptoms in combination with tree nut storage protein allergen molecule sensitization (Cor a 9, Cor a 14, Ana o 3 or Jug r 1) at 24 years in relation to early-life factors are shown in Table 3. In the univariate crude analysis, all tested early-life factors were significantly associated with tree nut storage protein sensitization more than twenty years later, with the highest point estimate noted for milk allergy (defined as specific symptoms and sensitization) at 4 years. However, after adjustment for the other covariates, only eczema up to two years, egg allergy and asthma at 4 years remained significant (Table 3). The same associated factors with the addition of milk allergy at 4 years were found when changing the outcome to only tree nut storage protein sensitization at 24 years of age (with or without reported symptoms), Table S2. We further evaluated timing of eczema, treatment of topical steroid and Filaggrin mutation status with univariate logistic regression (multiple logistic regression was not possible due to collinearity between the covariates), see Table S3. All different phenotypes for eczema were associated with both tree nut storage protein sensitization and in combination with reported tree nut symptoms, with the highest odds ratios observed for early doctor’s diagnosed eczema up to one year of age (OR 9.74, 95% CI 5.37–17.7). However, we saw no certain association between Filaggrin mutation status and any of the outcomes.

We also compared allergic phenotype factors among the 79 tree nut storage protein sensitized individuals with 400 tree nut extract sensitized individuals, but without sensitization to the storage proteins Cor a 9, Cor a 14, Jug r 1 or Ana o 3 (Table 4). The storage protein sensitized group showed several signs of more extensive allergic disease with significantly higher prevalence of severe asthma, adrenaline autoinjector use and elevated exhaled nitric oxide. However, lung function measures did not differ between the groups.

### 4 | DISCUSSION

In this large population-based cohort study, for the first time the prevalence rates of sensitization to tree nuts and tree nut allergens are presented among young adults from a general population from Northern Europe. We found that the prevalence of sensitization in combination with reported symptoms to tree nuts (hazelnut, walnut, pecan, cashew, pistachio, almond, Brazil nut) was 7.9% and 4.3% when excluding mild symptoms (OAS). The prevalence of sensitization to any of the analysed tree nut storage protein was 3.5%. Egg allergy, eczema and asthma at pre-school age were associated with tree nut symptoms and storage protein sensitization. We also confirm that allergen molecules are better diagnostic tools for prediction of allergic symptoms to hazelnut, walnut and cashew compared to analysing extract sensitizations. Furthermore, we show that tree nut storage protein sensitized individuals present a more extensive atopic phenotype than those with tree nut extract sensitization only.

We found that almost all individuals sensitized to hazelnut extract were also sensitized to birch and only few were sensitized to the allergens associated with more explicit symptoms, that is Cor a 14 and Cor a 9. In fact, the majority of the participants sensitized to hazelnut did not report any symptoms to hazelnut and were sensitized only to Cor a 1, a molecule that is closely related to birch pollen and hence is predicted to induce mild (OAS) to no symptoms. Thus, most tree nut-sensitized individuals have no clinical tree nut allergy. This has important general implications since birch trees are dominating in Northern Europe where a large proportion of the population is
sensitized to birch.\textsuperscript{19} Similar results have been reported from a previous study where 84\% of birch sensitized subjects were co-sensitized to hazelnut, 71\% to almond and 60\% to peanut. However, the majority of the nut-sensitized patients (71\% hazelnut, 83\% almond, 73\% peanut) reported no or mild symptoms.\textsuperscript{19} In this study, we present diagnostic tools to contribute to reducing over-diagnosis of hazelnut allergy. In our cohort, the prevalence of reported symptoms combined with sensitization to any tree nut was 7.9\%. If excluding the group that only had OAS, the prevalence dropped to 4.3\%. This is in line with the findings summarized in a systematic review of tree nut allergy, which only had OAS, the prevalence dropped to 4.3\%. This is in line with findings from other studies.\textsuperscript{5,21}

Another interesting finding was that the probability of reported tree nut allergy increased with an increasing degree of polysensitization to both tree nut extracts and allergen molecules. The increase was steeper for the storage protein allergen molecules Cor a 9, Cor a 14, Jug r 1 and Ana o 3 than for the larger group of tree nut extracts, implying the higher specificity of the allergen molecules compared to the extracts. To our knowledge, this finding has not been described elsewhere for tree nut allergy as it has for allergy to furred animals.\textsuperscript{24,25}

Early eczema, egg allergy and asthma were found to be factors significantly associated with an increased risk of tree nut storage protein sensitization at 24 years of age. These findings are in line with previous studies. One study suggested that patients with tree nut allergy seem to have more allergic comorbidities than the general population and showed that in their tree nut allergic cohort, 66\% had atopic dermatitis, 67\% had allergic rhinitis and 66\% had asthma.\textsuperscript{26} Another study found that after adjusting for each food allergy, environmental allergies and family history of asthma, children with tree nut allergy had significantly higher risk of asthma.\textsuperscript{27} In our study, the participants sensitized to any of the specific tree nut storage proteins Cor a 9, Cor a 14, Jug r 1 and Ana o 3 showed several signs of more extensive allergic disease with significantly higher prevalence of asthma, adrenaline autoinjector use and elevated exhaled nitric oxide, than the group sensitized to tree nut extract only. However, lung function measures were similar between the two groups. Our results are in line with a previous study showing that sensitization to some storage proteins including Cor a 9 and 14 in young patients with asthma was associated with asthma morbidity and higher levels of both systemic and local inflammation markers, compared to asthmatics not sensitized to these tree nut storage proteins.\textsuperscript{28}

\section*{4.1 Strengths and limitations}

One of the major strengths of this study is the high quality of the longitudinally collected data. A large group of individuals have been

\begin{table}[h]
\centering
\begin{tabular}{|c|c|c|c|c|c|c|c|}
\hline
 & \multicolumn{2}{c|}{Tree nut storage protein allergen molecule sensitization at 24y} & \multicolumn{2}{c|}{Tree nut sensitized at 24y without storage protein sensitization} \\
\hline
 & N=79 & \% & N=400 & \% & p-value \\
\hline
Eczema 24y & 38/79 & 48.1\% & 129/398 & 32.4\% & 0.0096 \\
Rhinoconjunctivitis 24y & 58/79 & 73.4\% & 328/398 & 82.4\% & 0.063 \\
Asthma 24y & 37/79 & 46.8\% & 94/398 & 23.6\% & <0.0001 \\
Severe asthma 24y & 4/79 & 5.1\% & 13/399 & 3.3\% & 0.0223 \\
Adrenalin use<12 months' & 4/79 & 5.1\% & 0/395 & 0\% & <0.0001 \\
FEV1<80\% of predicted (pre) & 4/69 & 5.8\% & 12/369 & 3.3\% & 0.30 \\
FEV1 reversibility>12\% & 1/65 & 1.5\% & 3/352 & 0.9\% & 0.14 \\
FEV1/FVC ratio<0.7 & 1/69 & 1.5\% & 12/369 & 3.3\% & 0.0028 \\
FENO>20 & 44/66 & 66.7\% & 118/337 & 35.0\% & <0.0001 \\
FENO>35 & 25/66 & 37.9\% & 53/337 & 15.7\% & <0.0001 \\
\hline
\end{tabular}
\caption{Comparison between 24-year-old participants sensitized to the tree nut storage proteins Cor a 9, Cor a 14, Jug r 1 or Ana o 3 (≥0.1 kU/L) and participants with tree nut sensitization but without sIgE-ab to any of these storage proteins.}
\end{table}
followed from birth to young adulthood with regard to different aspects of allergic disease and related risk factors. The dropout rate was low and on the final follow-up at 24 years as many as 2,215 participants provided both a blood sample and a completed questionnaire. This study of tree nuts is therefore unique in terms of the volume and the quality of the underlying data set.

Because of the large number of children investigated in this cohort, it was not possible to verify tree nut symptoms with double-blind placebo-controlled food challenges, and hence an overestimation of tree nut symptoms. In our data collection, we noticed that some of the participants seemed to have had trouble remembering why they avoided tree nuts at 24 years of age and did therefore not specify any symptoms—even though they did avoid tree nuts. In order to adjust for this problem, it was concluded that for an individual to be evaluated as having allergic symptoms, he or she must have confirmed symptoms in at least one of the questionnaires at age 24, 16 or 12. Another limitation was that symptoms to some tree nuts were not asked for separately, for example cashew/pistachio and walnut/pecan, and for Brazil nut we had no reported symptom data.

4.2 | Clinical implications and conclusions

Our study reveals that most extract-based tree nut-sensitized individuals do not have tree nut allergy but are solely birch pollen sensitized. The study also confirms that sIgE-ab to tree nut storage proteins are the best markers for specific tree nut allergy symptoms and storage protein sensitized individuals also showed several signs of more extensive allergic disease as compared to tree nut extract sensitized individuals, even in a population-based setting.

Taken together, this study increases the understanding of tree nut allergy in a general population, followed from infancy up to young adulthood, regarding prevalence, associated factors and polysensitization.

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CONFLICT OF INTEREST

No author has any conflict of interest to disclose except the following: Dr. Borres is an employee of Thermo Fisher Scientific, Uppsala, Sweden; Dr. Ballardini reports personal fees from Sanofi Pfizer and Galenica, outside the submitted work; Dr. Konradsen reports that he has received support (laboratory material and analytical support) from Thermo Fisher Scientific in other research projects, but no support related to the current project; Dr Westman reports personal fees from Thermo Fisher Scientific, outside the submitted work; Dr. Asarnoj reports personal fees from Orion Pharma and Mylan, outside the submitted work.

AUTHOR CONTRIBUTIONS

All authors have approved the last version before submission. Jessica Bager, Anna Asarnoj and Sandra Tedner participated in design of the study, data analysis and manuscript writing. Niklas Andersson contributed with statistical support, managing of the database, critically reviewed data and revised the manuscript. Natalia Ballardini, Magnus P. Borres, Jon R Konradsen, Caroline Nilsson and Marit Westman critically reviewed data and revised the manuscript. Inger Kull and Anna Bergström served as Co-Principal investigator (co-PI) of the BAMSE study, participated in design of the study, critically reviewed data and revised the manuscript. Marianne van Hage is responsible for IgE analyses in the project, critically reviewed data and revised the manuscript. Erik Melen served as Principal investigator (PI) of the BAMSE study, participated in design of the study, critically reviewed data and revised the manuscript.

ETHICAL APPROVAL

Ethical approval was obtained from the Swedish Ethical Review Authority (2016/1380-31/2).

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION
Additional supporting information may be found online in the Supporting Information section.

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