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Title: IgE-antibodies in relation to prevalence and multimorbidity of eczema, asthma and rhinitis from birth to adolescence

Short title: IgE-sensitization in childhood

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ABSTRACT

Background: Eczema, asthma and rhinitis affect a large proportion of children but their prevalence varies with age. IgE-antibodies are also common in the paediatric population. However, the links between IgE, disease and trajectories are unclear.

Objective: To better understand the links between sensitization and disease, we studied IgE-sensitization ever in relation to eczema, asthma and rhinitis, in children followed up to 16 years of age.

Methods: From the Swedish population-based birth cohort BAMSE, 2,607 children were included. Parental reports from six time points between 1 and 16 years were used to identify children with eczema, asthma and rhinitis. Blood was collected at 4, 8 and 16 years and sensitization ever was defined as allergen-specific IgE ≥ 0.35 kU_A/L to common food and/or inhalant allergens at any time point. Odds ratios for eczema, asthma, rhinitis and multimorbidity in relation to sensitization ever were calculated using generalized estimating equations.

Results: Fifty-one percent were sensitized at least once up to 16 years. Almost a quarter of ever-sensitized children did not have any disease. After adjustment for potential confounders, sensitization ever was significantly associated with; i) eczema throughout childhood, ii) multimorbidity of eczema, asthma and rhinitis from 1 to 16 years (OR for multimorbidity: 5.11, 95% CI; 3.99-6.55), iii) asthma and rhinitis from 4 to 16 years of age.

Conclusions: Specific IgE is strongly associated with eczema and allergic multimorbidity throughout childhood and with asthma and rhinitis from age 4 years. However, 23% of children with IgE-sensitization do not develop any disease in childhood.

INTRODUCTION

Eczema, asthma and rhinitis are common in the paediatric population. Fifty-eight percent of children in the population-based BAMSE birth cohort have had eczema, asthma or rhinitis up to 12 years.(1) Almost half of the US population aged 6 years and older are sensitized to at least one allergen and of children aged 1 to 5 years, one of three are sensitized to 1 or more allergens.(2) Even though there is a strong and consistent association between IgE-sensitization and eczema, asthma and rhinitis (3) these diseases also exist in non-sensitized individuals. In addition, sensitization is found among individuals without allergy-related diseases.(4)

Sensitization has been shown to precede disease development.(5, 6) However, advances in the field of eczema research (7-10) have questioned this temporal association between sensitization and disease suggesting that disease may precede and influence IgE-sensitization. The association between IgE-sensitization and disease has been extensively studied. However, data is lacking concerning how IgE reactivity ≥ 0.35 kU_A/L, at any time point during childhood, influences development of eczema, asthma and rhinitis and allergic multimorbidity in childhood and adolescence. Birth cohorts with data on symptoms and specific IgE to common food and inhalant allergens are able to answer gaps in our knowledge.

The aim of this study was to evaluate occurrence of any sensitization ever defined as allergen-specific IgE ≥ 0.35 kU_A/L to common food and/or inhalant allergens at 4, 8 and/or 16 years and its association to eczema, asthma and rhinitis and multimorbidity of these diseases

up to 16 years using both a cross-sectional and a longitudinal approach. For this purpose we used data from our population-based BAMSE birth cohort. We hypothesised that the vast majority of children with allergen-specific IgE at some time during childhood would have eczema, asthma or rhinitis at some period up to 16 years of age.

MATERIAL AND METHODS

Study subjects

The BAMSE project is a population-based cohort from Stockholm, Sweden in which new-born children were consecutively recruited from 1994 to 1996 and followed up to 16 years of age. The BAMSE cohort comprised 4,089 infants, corresponding to 75% of the eligible subjects (Figure E1).(11) When the children were two months (baseline) parents completed questionnaires on background factors. When the children were 1, 2, 4, 8, 12 and 16 years questionnaires regarding symptoms of eczema, asthma and rhinitis were answered. At the 16-year follow-up 78% still remained in the cohort. For a majority of children blood was collected at ages 4, 8 and 16 years and plasma was analysed for allergen-specific IgE-antibodies.

Definitions

Background variables

Previously identified background variables for the development of allergy-related diseases were used in the present analyses.(12-15) These are described in table E1.

Sensitization

The ImmunoCAP System (Thermo Fisher Scientific, Uppsala, Sweden) was used with the technical cut off 0.35 kU_A/L, as recommended by the manufacturer.

Sensitization ever was defined as allergen-specific IgE ≥ 0.35 kU_A/L to a mix of common inhalant allergens with Phadiatop[®] (cat, dog, horse, birch, timothy, mugwort, *Dermatophagoides pteronyssinus* and *Cladosporium herbarum*) and/or to a mix of common food allergens with fx5[®] (milk, egg, cod, soy, peanut, and wheat) at one or more of the follow-ups at 4, 8 and 16 years.

Never-sensitized was defined as allergen-specific IgE < 0.35 kU_A/L to Phadiatop and fx5 at all time points.

Allergy-related disease outcomes

Assessment of allergy-related diseases was based on the follow-up questionnaires at age 1, 2, 4, 8, 12 and 16 years as previously described in BAMSE:

Eczema – at age 1, 2 and 4 years: dry skin, itchy rashes with age-specific location for two weeks or more the year before follow-up and/or doctor's diagnosis of eczema since the last follow-up.(16) Eczema – at age 8 and 16 years; dry skin in combination with itchy rash and typical localization the year before follow-up and/or doctor's diagnosis of eczema since the last follow-up. Eczema – at age 12 years: dry skin in combination with itchy rash and typical localization the year before follow-up and/or doctor's diagnosis of eczema since the age of 10 years.(17)

Asthma – at age 1 and 2 years: at least three episodes of wheeze in combination with inhaled glucocorticoids and/or signs of bronchial hyperreactivity without concurrent upper respiratory infection the year before follow-up.(18) Asthma – at age 4, 8, 12 and 16 years; at least four episodes of wheeze the year before follow-up or at least one episode of wheeze in combination with occasional or regular use of prescribed inhaled glucocorticoids.(13)

Rhinitis – at age 1, 2, 4, 8, and 16 years: symptoms of sneezing, a runny or blocked nose, or itchy, red and watery eyes after exposure to furred pets or pollen the year before follow-up and or doctor's diagnosis of allergic rhinitis since the last follow-up. Rhinitis – at age 12 years: symptoms of sneezing, a runny or blocked nose, or itchy, red and watery eyes after exposure to furred pets or pollen the year before follow-up and or doctor's diagnosis of allergic rhinitis since the age of 10 years.(19)

Multimorbidity was defined as having at least two of the diseases eczema, asthma or rhinitis at the same follow-up.

Statistics

Chi-square tests were used for evaluation of differences between ever and never sensitized children for dichotomous variables. For evaluation of differences in presence of disease up to 16 years Wilcoxon's rank sum test was used and missing data were regarded as no disease. The proportion of children with missing data ranged between 1-7% and a sensitivity analysis including only children that had participated at all follow-ups (n=2,312) showed that missing data did not influence the results. For evaluation of differences in median levels of IgE between ever-sensitized children with and without disease quantile regression was used.

Generalized estimating equations (GEEs)(20) with an unstructured correlation matrix were used to assess the impact of sensitization ever on the risk of eczema, asthma, rhinitis and multimorbidity over time. Adjustment was made for sex, parental allergy, exclusive breastfeeding <4 months, maternal smoking during pregnancy and at enrolment, low socioeconomic status and young mother (< 26 years). We evaluated possible interaction for sex and parental allergy but no effect modification was found. All statistical analyses were performed with STATA Statistical Software (release 11.1; StataCorp, College Station, TX, USA).

RESULTS

Demographic characteristics

The study population consisted of 2,607 children who provided blood at least at two of three follow-ups (Figure E1). When comparing the study population to the original cohort (N=4,089) minor differences were seen for background factors (Table E2). Fifty-one percent of the children (1,328 of 2,607) had allergen-specific IgE ≥ 0.35 kU_A/L at one or more follow-ups and thus were classified as ever-sensitized. Background characteristics for ever and never sensitized children are shown in Table E2. Of the 1,328 ever-sensitized children 40% were sensitized at one occasion only, 24% at two occasions and 36% were sensitized at all three follow-ups at 4, 8 and 16 years.

Sensitization ever in relation to eczema, asthma and rhinitis

Of the ever-sensitized children, 76.7% (1,018 of 1,328), had had eczema, asthma, or rhinitis at some time during the follow-up period, whereas 48.4% (619 of 1,279) reported these outcomes among non-sensitized children ($p < 0.001$), (Figure 1). The 310 ever-sensitized

children without disease were compared to ever sensitized children having had eczema, asthma or rhinitis. Ever sensitized children without disease had less parental allergy compared to ever sensitized children with disease (37.1% vs. 53.3%, $p<0.001$), but otherwise no significant differences were found regarding background factors. Prevalence rates of sensitization, median concentrations and IQR for allergen-specific IgE levels to food and airborne allergens at the three time points for ever sensitized children with and without disease are shown in Table I. Ever sensitized children without disease had lower allergen-specific IgE compared to ever sensitized children with disease (Table I).

The proportion of ever sensitized children with eczema, asthma or rhinitis increased with age. At age 1 year 28% of the ever sensitized children presented with eczema, asthma or rhinitis and at 16 years 51% of the ever sensitized children had eczema, asthma or rhinitis (Figure 2). The proportion of children with allergy related disease but without sensitization ranged from 12% to 22% at the different follow-ups (Figure 2).

Eczema was significantly more prevalent among ever sensitized children at all ages compared to never sensitized children (Table II). There were no significant differences between ever and never sensitized children regarding prevalence of asthma and rhinitis in infancy, but from 4 years of age asthma and rhinitis were significantly more prevalent among ever sensitized children compared to never sensitized children (Table II). Fifty-two percent (693 of 1,328), of ever sensitized children had been sensitized both to foods and to airborne allergens. The prevalence of eczema, asthma and rhinitis was markedly higher in the group with sensitization to both foods and airborne allergens compared to children with sensitization to foods only (205 of 1,328, 15%) or to airborne allergens only (490 of 1,328, 37%), Figure E2.

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These differences were significant at all ages for all diseases with the exception for asthma at 1 year (rhinitis at 1 year; $p=0.010$, asthma at 2 years; $p=0.033$, all other $p<0.001$). Rhinitis was significantly more prevalent from 4 to 16 years in the group sensitized to airborne allergens only compared to the group sensitized to foods only (rhinitis at 4 years; $p=0.035$, all other $p<0.001$). Also asthma and eczema tended to be more prevalent among children sensitized to airborne allergens only compared to children sensitized to foods only, Figure E2.

The proportion of children in the study population with eczema, asthma, rhinitis and any disease at the follow-ups at 1, 2, 4, 8, 12 and 16 years are presented in Figure E3. Figure E4 shows the number of ever and never sensitized children that had eczema, asthma, rhinitis and any of the diseases during the follow-up time. In addition, Figure E4 illustrates at how many follow-ups the children had the diseases. Ever sensitized children had eczema and rhinitis at significantly more follow ups compared to never sensitized children (both $p<0.001$), however there was no significant difference regarding asthma, Figure E4. Finally, we compared ever and never sensitized children who had any allergy-related disease and explored at how many of the follow-ups they had been affected by eczema, asthma or rhinitis. Of the ever sensitized children having had any disease, more than half had had eczema, asthma or rhinitis at three or more of the six follow-ups compared to only one of four of the children without sensitization, $p<0.001$ (Figure E4). Among children with eczema ever, 61.0% were sensitized at some time point, while the corresponding proportions among children with asthma and rhinitis ever were 67.2% and 78.0%, respectively.

Multimorbidity in relation to sensitization ever

Figure 2 also shows the degree of multimorbidity among ever and never sensitized children at each follow-up. Multimorbidity at the different ages ranged from 1.6% to 2.9% among children never sensitized while the corresponding range of multimorbidity for ever sensitized children was 3.4% to 13.7%. Multimorbidity increased with age among ever sensitized children and was significantly more common at all ages compared to never-sensitized children ($p=0.003$ at age 1 year, all other $p<0.001$). We compared the group sensitized to airborne allergens only ($n=490$) to those sensitized only to foods ($n=205$) and found a significantly higher prevalence of multimorbidity from 8 years of age in the group sensitized to airborne allergens, $p=0.008$ at 8 years, $p=0.006$ at 12 years and $p=0.002$ at 16 years, Figure E2. Children sensitized to both foods and airborne allergens ($n=693$) displayed significantly more multimorbidity at all ages compared to children sensitized to foods or airborne allergens only, all $p<0.001$.

Adjusted longitudinal analysis of the association between sensitization ever and eczema, asthma, rhinitis and multimorbidity up to age 16 years

Adjusted longitudinal analysis was performed to evaluate the associations between sensitization ever and eczema, asthma, rhinitis and multimorbidity of the diseases at different ages during childhood. Figure 3 shows the associations presented as Odds Ratios (ORs) between sensitization ever and eczema, asthma, rhinitis and multimorbidity at the ages 1, 2, 4, 8, 12 and 16 years. Sensitization ever was significantly associated with eczema throughout childhood with the strongest association the very first year of life.

Sensitization ever was not associated with asthma or rhinitis in infancy, but from 4 years of age ORs were increased for both diseases. Furthermore, sensitization ever was significantly associated with multimorbidity of eczema, asthma and rhinitis at all ages (Figure 3) resulting in an overall OR of 5.11 (95% CI; 3.99-6.55).

DISCUSSION

In this population-based cohort study of 2,607 children followed prospectively from birth, as many as 51% were sensitized at least once up to 16 years of age. Almost a quarter of the ever-sensitized children were asymptomatic, i.e. they did not have eczema, asthma or rhinitis during childhood. In the group of ever sensitized children the proportion with disease increased with age. After adjustment for potential confounders, sensitization ever was significantly associated with; i) eczema throughout childhood, ii) multimorbidity of eczema, asthma and rhinitis from 1 to 16 years, iii) asthma and rhinitis from 4 to 16 years of age.

The strengths of this study are the large number of participants, the prospective design and that the children were followed up regularly from birth to 16 years. We measured allergen-specific IgE-antibodies in serum with ImmunoCAP to six food and eight airborne allergens with a technical cut off ≥ 0.35 kU_A/L to define sensitization ever. This cut off enables comparison with other studies. In addition, classification of sensitization ever was based on at least two, and for most children three blood samples collected at different time points during childhood and adolescence. The population-based design, with inclusion of 75% of eligible subjects born in representative areas of Stockholm, and the high follow-up rate contributes to generalizability of the results. A weakness is that we do not have information on sensitization during the first three years of life. Thus, it is plausible that some children with transient

sensitization to food early in life were classified as not sensitized which may have diluted our results.

The proportion of children classified as ever sensitized in our study was 51%. Even though there are several population based birth cohorts that have evaluated sensitization repeatedly we have not been able to find corresponding figures of sensitization ever. However, rates of sensitization at each follow up in BAMSE(21) are consistent with findings from other European studies(22-24) and also comparable to the recently published NHANES study including more than 10,000 subjects from the US population showing that 44.6% in the study population aged six years or older were sensitized.(2)

Allergic sensitization as well as eczema, asthma and rhinitis are very common in childhood, and we hypothesised that the vast majority of children with IgE-sensitization, regardless of when, would have eczema, asthma or rhinitis at some time during childhood. However, we found that almost one of four ever-sensitized children never had had eczema, asthma or rhinitis, corresponding to 12% of all children in this population-based cohort followed up to 16 years. When comparing the ever sensitized children with and without disease, the group without disease was characterized by significantly less parental allergy. Thus, it seems that genetic and/or environmental factors that influence expression of IgE are partly different from those involved in the development of allergy-related diseases during childhood. This is in line with genetic studies suggesting both shared and unique genetic factors for IgE vs. allergy-related disease.(25)

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It would be interesting to follow up the ever-sensitized individuals without disease. IgE responses may start years before disease onset which have been shown for rhinitis.(6, 26) Also a recent publication based on our material found an increased risk of abdominal pain at 12 years in children sensitized to food allergens at 4 or 8 years. A stratified analyses showed that this was confined to children whose parents did not report symptoms of food hypersensitivity of the child at time of sensitization.(27) Thus, it is possible that sensitized children without classical allergy-related diseases experience other insidious symptom that remains to be explored.

It has recently been shown that sensitization among children having either eczema, asthma or rhinitis can explain 38% of future allergic comorbidities.(28) Also, a recent publication from the Isle of Wight study that followed children from birth to 18 years showed strong associations between comorbidities for eczema, asthma and rhinitis and concurrent allergic sensitization.(4) In addition, we have shown that sensitization ever is significantly associated with allergic multimorbidity at all ages including infancy, even though allergic rhinitis and allergic asthma are rare at that age. Further studies are needed to disentangle whether this association is merely a result of sensitization in infancy with immunologic responses to allergens causing eczema, asthma and rhinitis. Or if the increased risk for multimorbidity in infancy among children with a propensity to produce allergen-specific IgE rather reflects a diathesis including both a propensity to produce allergen-specific IgE and to develop eczema, asthma and rhinitis.

The concept of the atopic march, with progression of allergic diseases from eczema in infancy to asthma and rhinitis later in life, is widely used, although sometimes disputed.(29-33) A recent study in two population-based birth cohorts, that used Bayesian machine learning methods to identify individual profiles of eczema, wheeze and rhinitis, found that only 7 % of children with symptoms follow trajectory profiles resembling the atopic march and sensitization measured at 8 years did not discriminate these children.(34) However, in our study sensitization ever was associated with eczema throughout childhood with the strongest association the first years of life, whereas the association with asthma and rhinitis was seen first at 4 years and increased to 16 years. Also, in contrast to never sensitized children, the group of ever sensitized children developed more symptoms with increasing age. Thus, even though evaluation of individual profiles remains to be explored in our cohort, we have shown that at a group-level, IgE-sensitization ever includes development of disease in accordance with the atopic march, while that seems not to be the case in never sensitized children.

The temporal association between IgE-sensitization and disease was beyond the scope of this study. However, recent years discoveries concerning filaggrin mutations and skin barrier defects, and their possible role for sensitization (7, 35-37) in conjunction with the strong association of eczema from 1 year of age with sensitization from 4 years found in our study awake the question whether the development of eczema is a consequence of production of IgE-antibodies as described by the current definition of atopy (38) or if it's rather the other way around, or possibly a combination of both.

In conclusion, propensity to produce IgE is strongly associated with eczema and multimorbidity throughout childhood and with asthma and rhinitis from 4 to 16 years of age. However, one of four children who produce IgE does not develop any allergy-related disease up to age 16 years.

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Contributors: MW initiated the BAMSE cohort. IK and EH coordinated the data collection. NB, MW, IK, MvH, AB, JMA, EM, CFW and JB designed the current study. NB and MW analysed the data. All authors had full access to all of the data and participated in the interpretation of the findings. NB and MW wrote the initial draft. All authors participated in critical revision of the manuscript and provided important intellectual input and approved the final version. MW is the guarantor.

Conflict of interest disclosures: None declared

Ethical approval: The study was approved by the regional ethics committee, Karolinska Institute, Stockholm and participants gave written informed consent.

Supportive information:

Figure E1. Flow chart of the BAMSE birth cohort and the current study

Figure E2. Prevalence of eczema, asthma, rhinitis and multimorbidity among children with sensitization ever to food only, to airborne allergens only and to both food and airborne allergens

Figure E3. Prevalence of eczema, asthma, rhinitis and any of the diseases at 1, 2, 4, 8, 12 and 16 years in the population-based birth cohort BAMSE

Figure E4. Occurrence of eczema, asthma, rhinitis and any of the diseases up to 16 years among ever-sensitized children and never-sensitized children in the BAMSE birth cohort.

Table E1. Definitions of background characteristics

Table E2. Distribution of background characteristics

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Figure legends

Figure 1

Flow chart of the current study. Included children provided blood for measurement of allergen-specific IgE at two or three of the follow-ups at the ages 4, 8 and 16 years.

Sensitization ever was defined as allergen-specific IgE ≥ 0.35 kU_A/L at least at once. No sensitization denotes that children had allergen-specific IgE < 0.35 kU_A/L for both Phadiatop and fx5 at all tests performed. Yellow fields represent children having had any of the diseases eczema, asthma or rhinitis up to the age of 16 years.

Figure 2

Eczema, asthma, rhinitis and multimorbidity of these diseases among ever- and never-sensitized children up to age 16 years in the BAMSE cohort. Venn-diagrams are proportional and overlapping fields represents multimorbidity.

Figure 3

Impact of sensitization ever on eczema, asthma, rhinitis and multimorbidity in childhood.

Calculations were based on 1,328 children classified as ever-sensitized that were compared to the reference group of 1,279 children with no sensitization. Sensitization ever was defined as

allergen-specific IgE ≥ 0.35 kU_A/L at any time point. Included children provided blood for measurement of allergen-specific IgE at two or three of the follow-ups at the ages 4, 8 and 16 years. Multimorbidity was defined as having at least two of the diseases eczema asthma and rhinitis.

*Odds ratios and 95% confidence intervals were calculated by using generalized estimating equations (GEE), adjusted for; sex, parental allergy, exclusive breastfeeding <4 months, maternal smoking, low socio-economic status and young mother (< 26 years).

TABLE I. Sensitization to food and airborne allergens at 4, 8 and 16 years among ever-sensitized children with and without disease (eczema, asthma and/or rhinitis) up to 16 years in the population-based BAMSE birth cohort

Airborne allergens*	Children with disease, n=1,018				Children without disease, n=310				P-value [‡]
	n	%	Median IgE kU _A /L	IQR	n	%	Median IgE kU _A /L	IQR	
4 yrs	331/891	37.1	2.93	1.0-10.1	24/276	8.7	0.55	0.46-1.1	0.020
8 yrs	544/929	58.6	10.0	1.7-32.5	61/274	22.3	0.85	0.6-1.8	<0.001
16 yrs	808/917	88.1	13.0	2.2-38.2	194/284	68.3	1.34	0.56-9.2	<0.001
Food allergens [^]	n	%	Median IgE kU _A /L	IQR	n	%	Median IgE kU _A /L	IQR	P-value [‡]
	n	%	Median IgE kU _A /L	IQR	n	%	Median IgE kU _A /L	IQR	
4 yrs	281/892	31.5	0.91	0.46-3.4	84/276	30.4	0.59	0.41-1.1	0.073
8 yrs	368/929	39.6	0.76	0.47-1.7	98/275	35.6	0.65	0.46-1.1	0.156
16 yrs	249/917	27.1	0.80	0.5-3.6	59/284	20.8	0.50	0.4-0.9	0.013

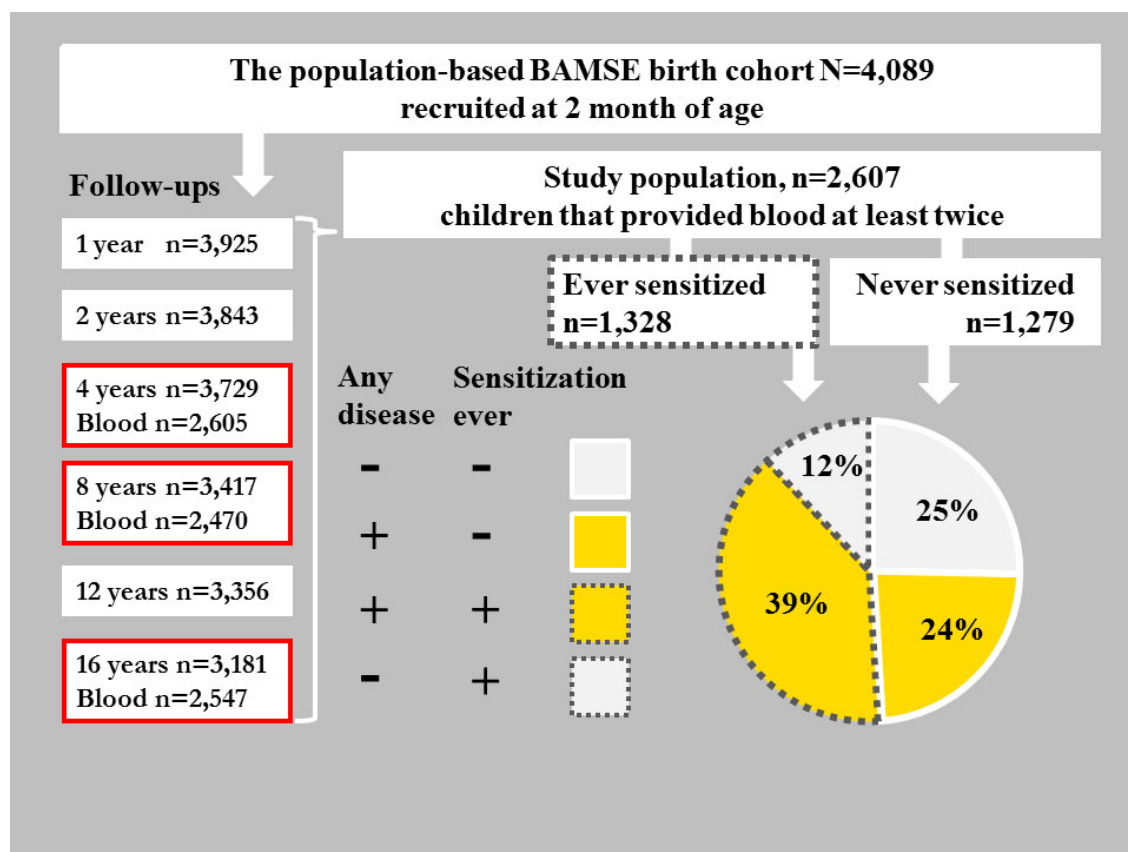
*specific IgE ≥ 0.35 kU_A/L to a mix of the inhalant allergens; cat, dog, horse, birch, timothy, mugwort, *Dermatophagoides pteronyssinus*, and *Cladosporium herbarum*

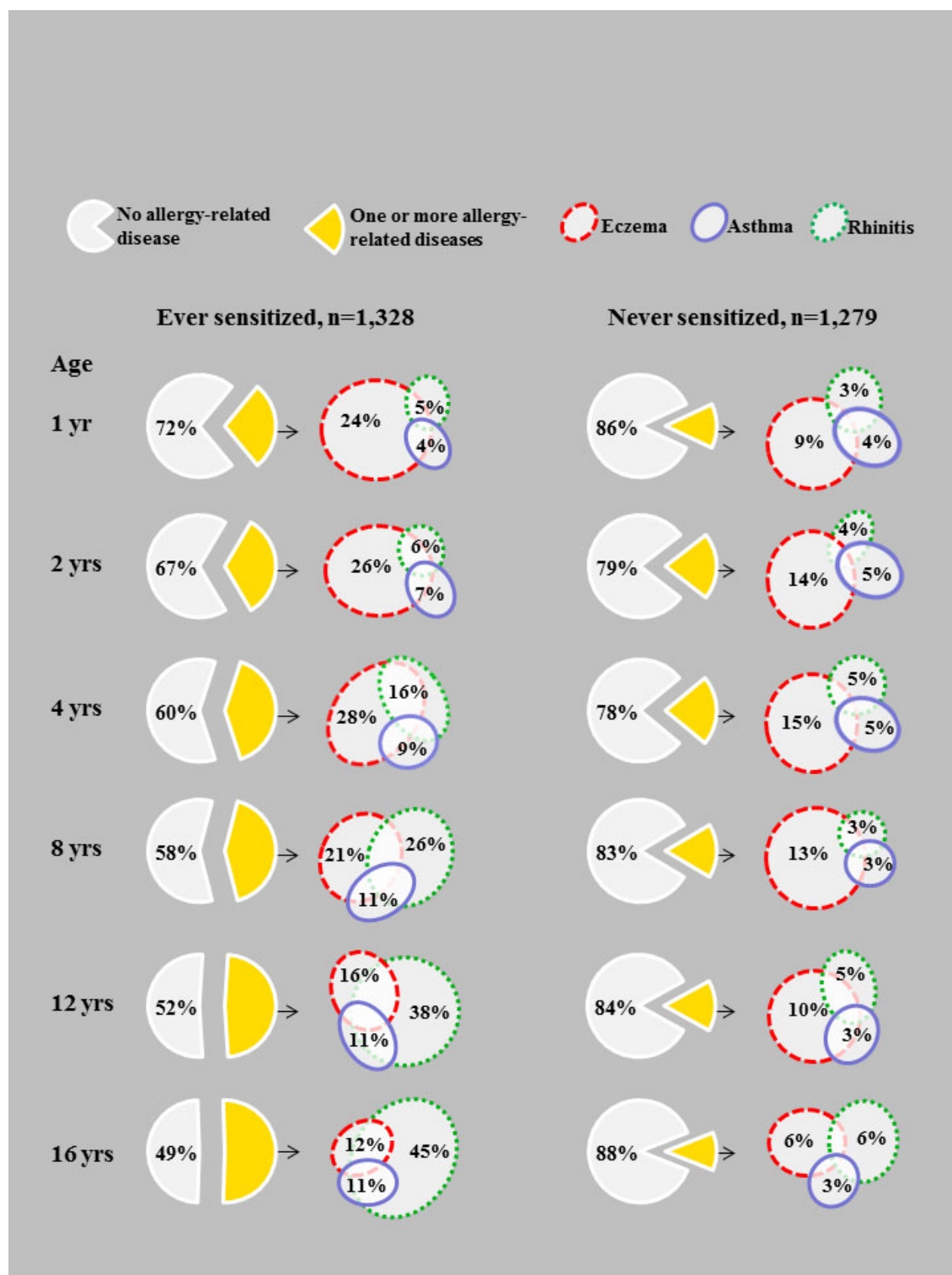
[^]specific IgE ≥ 0.35 kU_A/L to a mix of the food allergens; milk, egg, cod, soy, peanut, and wheat

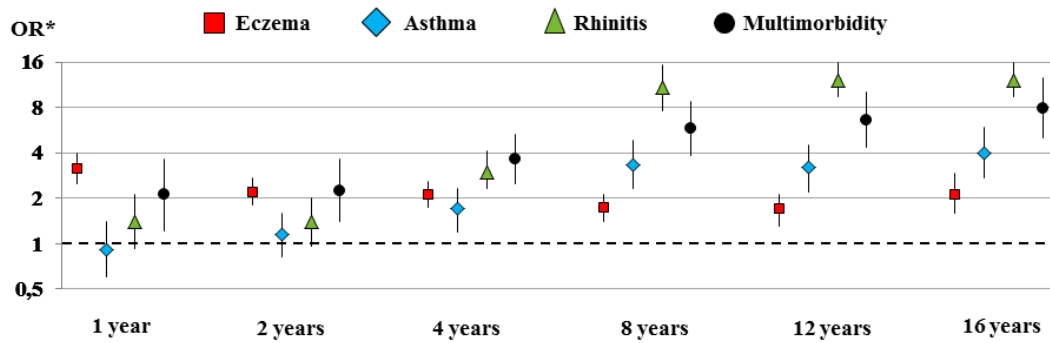
[‡]p-value for differences in median value of IgE was calculated by quantile regression

TABLE II. Prevalence of eczema, asthma and rhinitis up to 16 years among ever-sensitized and never-sensitized children in the BAMSE cohort (n=2,607)

	Ever sensitized, n=1,328				Never sensitized, n=1,279			
	Prevalence	95% CI	obs		Prevalence	95% CI	obs	
Eczema								
1 yr	23.7%	21.4% - 26.0%	1304		8.8%	7.3% - 10.4%	1258	
2 yrs	26.4%	24.0% - 28.8%	1306		14.0%	12.0% - 15.9%	1261	
4 yrs	27.8%	25.4% - 30.3%	1315		14.6%	12.7% - 16.5%	1267	
8 yrs	21.4%	19.2% - 23.7%	1269		13.2%	11.3% - 15.1%	1226	
12 yrs	15.9%	13.9% - 17.9%	1289		9.9%	8.2% - 11.6%	1225	
16 yrs	11.9%	10.1% - 13.7%	1264		5.7%	4.4% - 7.0%	1201	
Any time	51.1%	48.4% - 53.8%	1328		33.9%	31.3% - 36.5%	1279	
Asthma								
1 yr	3.8%	2.7% - 4.8%	1304		3.9%	2.8% - 5.0%	1259	
2 yrs	6.6%	5.2% - 7.9%	1304		5.3%	4.1% - 6.6%	1259	
4 yrs	9.5%	7.9% - 11.0%	1311		5.4%	4.2% - 6.7%	1258	
8 yrs	10.5%	8.8% - 12.2%	1295		3.4%	2.4% - 4.4%	1249	
12 yrs	10.5%	8.8% - 12.2%	1282		3.4%	2.4% - 4.5%	1221	
16 yrs	10.6%	8.8% - 12.3%	1251		2.6%	1.7% - 3.5%	1190	
Any time	26.3%	23.9% - 28.7%	1328		13.3%	11.4% - 15.2%	1279	
Rhinitis								
1 yr	4.7%	3.5% - 5.9%	1298		3.3%	2.3% - 4.2%	1257	
2 yrs	5.9%	4.6% - 7.2%	1301		4.0%	2.9% - 5.1%	1257	
4 yrs	16.2%	14.2% - 18.2%	1299		5.5%	4.2% - 6.8%	1253	
8 yrs	25.6%	23.3% - 28.0%	1299		3.1%	2.1% - 4.0%	1245	
12 yrs	37.9%	35.2% - 40.5%	1275		4.8%	3.5% - 6.0%	1200	
16 yrs	45.3%	42.6% - 48.1%	1253		6.0%	4.6% - 7.3%	1172	
Any time	56.9%	54.3% - 59.6%	1328		16.7%	14.6% - 18.7%	1279	







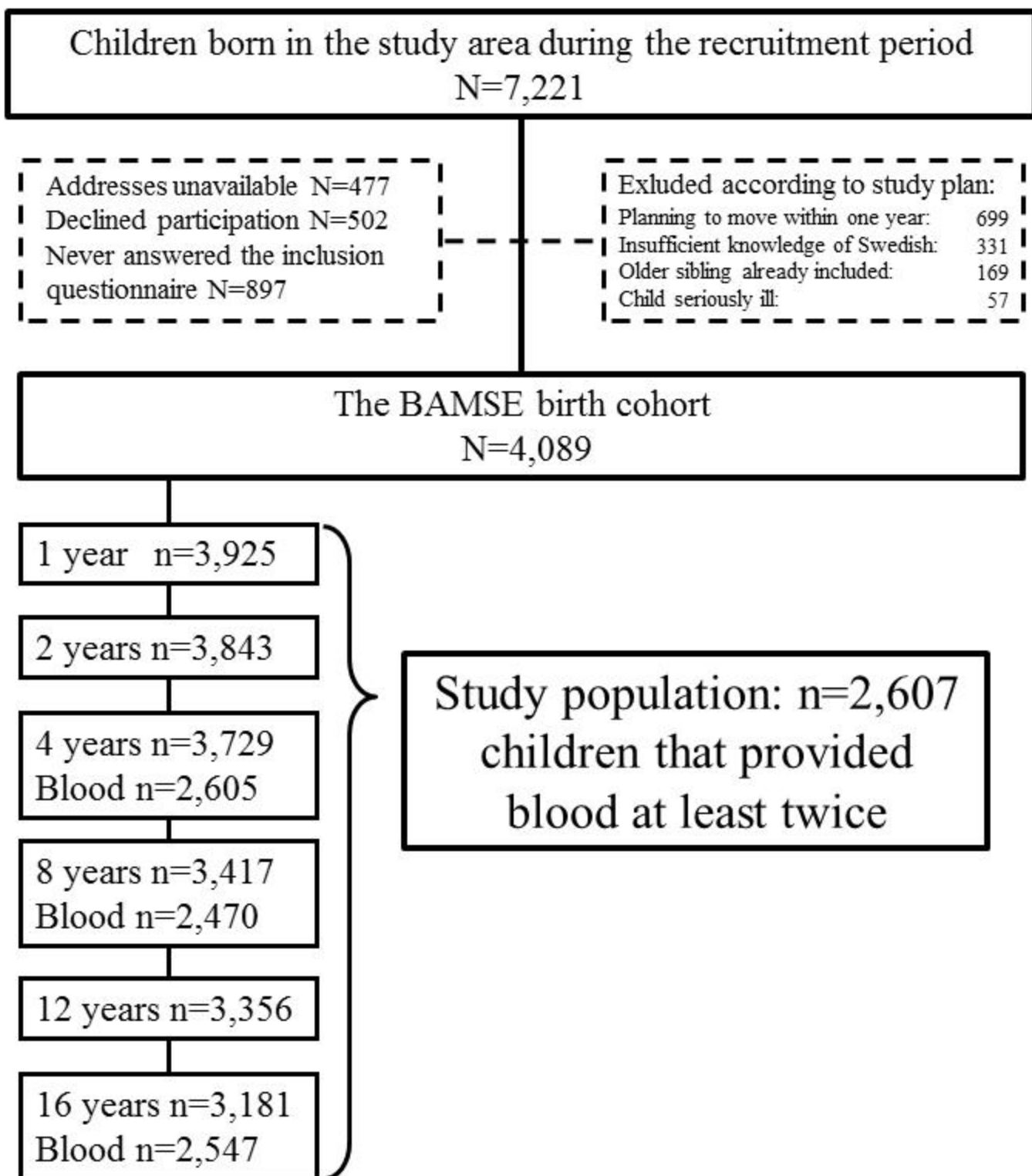


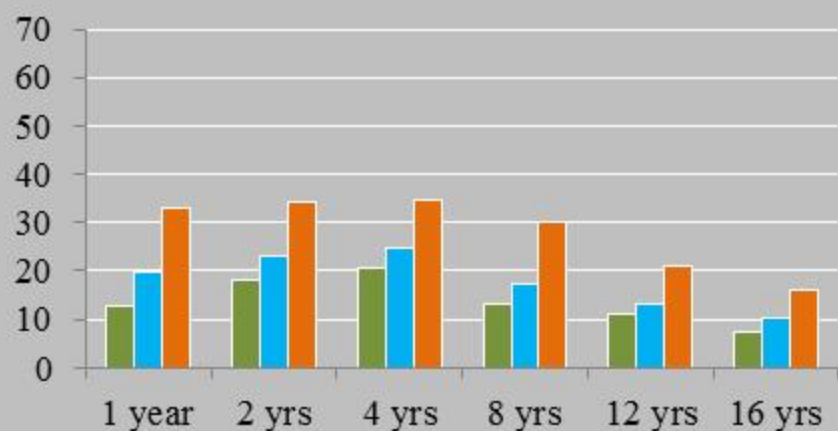
Figure E1

Flow chart of the BAMSE birth cohort and the current study

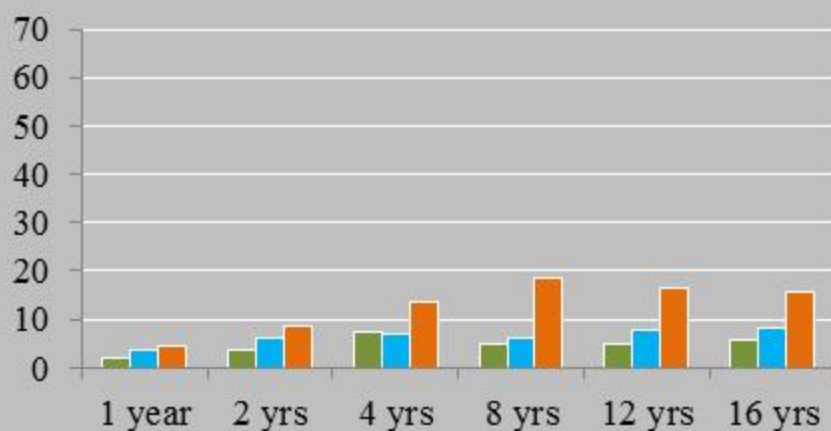
Figure E2

Prevalence of eczema, asthma, rhinitis and multimorbidity (having two or three of the diseases at the same follow up) at 1, 2, 4, 8, 12 and 16 years in the BAMSE birth cohort among children with sensitization ever to food only, to airborne allergens only and to both food and airborne allergens

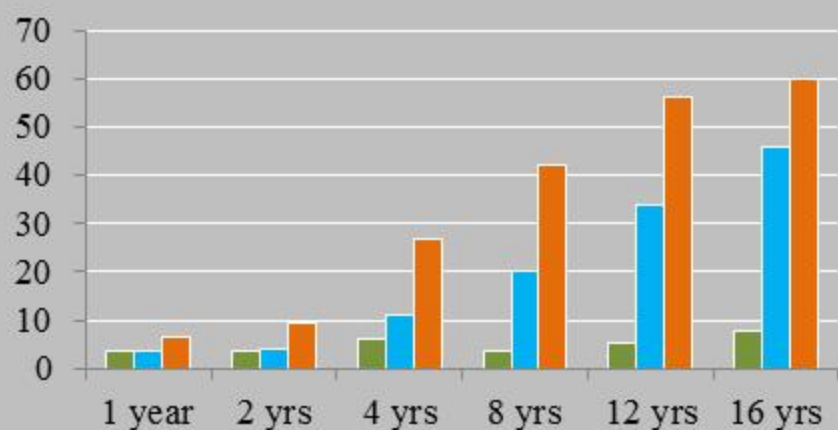
Eczema



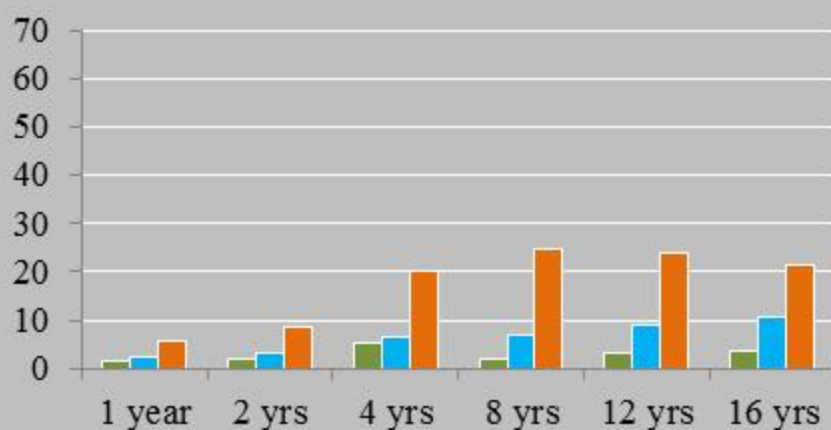
Asthma



Rhinitis



Multimorbidity



Sensitization to: ■ Food only (n=205) ■ Airborne allergens only (n=490) ■ Food and airborne allergens (n=693)

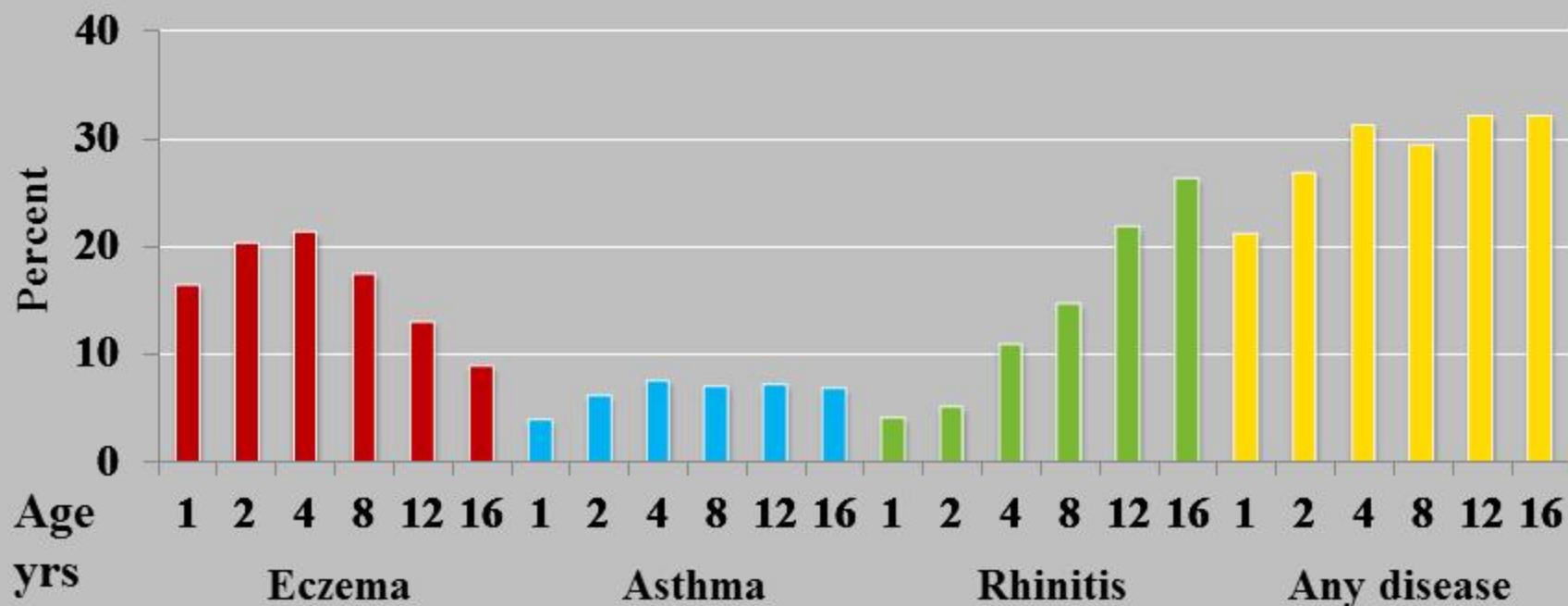


Figure E3

Prevalence of eczema, asthma, rhinitis and any of the diseases at 1, 2, 4, 8, 12 and 16 years in the population-based birth cohort BAMSE

Number of follow-ups with disease

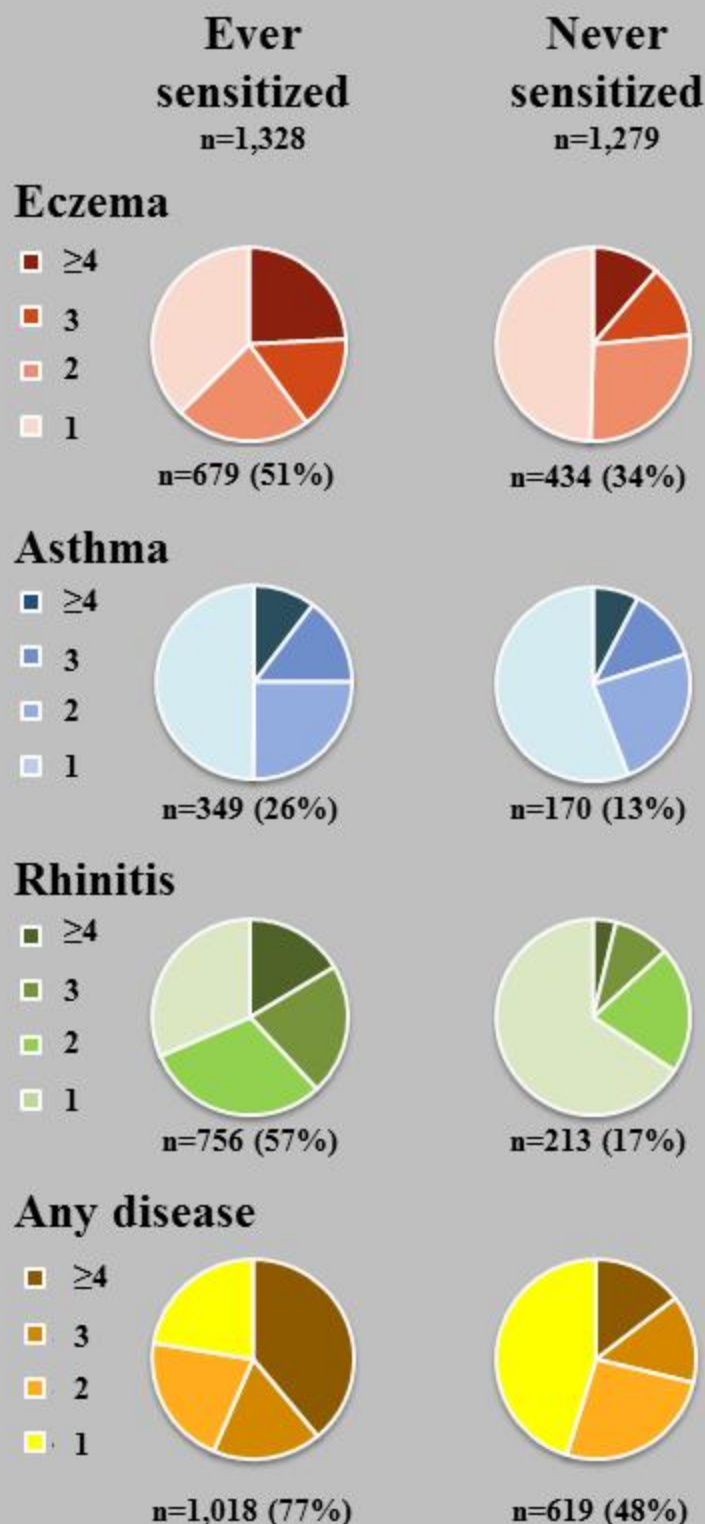


Figure E4

Occurrence of eczema, asthma, rhinitis and any of the diseases up to 16 years among ever- and never-sensitized children in the BAMSE birth cohort. Circles include children ever having had the disease and sections represent the proportion of children having had the disease at one, two, three or four or more of the follow ups at age, 1, 2, 4, 8, 12 and 16 years.

TABLE E1. Definitions of background characteristics

Background variable	Definition
Parental allergy	Mother and/or father with doctor's diagnosis of asthma and asthma medication and/or doctor-diagnosed hay fever in combination with allergy to furred pets and/or pollen and/or doctor's diagnosis of eczema at the time of enrolment.
Low socio-economic status	Both parents blue collar workers according to the Nordic standard occupational classification and Swedish socio-economic classification.
Exclusive breastfeeding	Children breastfed without exposure to formula or solid foods during the first four months of life.
Tobacco exposure	Mother smoked at least one cigarette per day during pregnancy or at the time of enrolment.
Young mother	Maternal age < 26 years at birth of the child.

TABLE E2. Distribution of background characteristics among children in the original cohort (N=4,089), children included in the present study (n=2,607), ever-sensitized children (n=1,328) and never-sensitized children (n=1,279) in the population based BAMSE birth cohort

	Total cohort		Included children			Ever sensitized			Never sensitized		
	n	%	n	%	95% CI	n	%	95% CI	n	%	95% CI
Sex											
male	2,065	50.5	1,298	49.8	47.9-51.7	708	53.3	50.6-56.0	590	46.1	43.3-48.9
Parental allergy											
yes	1,746	43.2	1,153	44.6	42.7-46.5	652	49.5	46.8-52.2	501	39.5	36.8-42.2
Socioeconomic status											
blue collar worker	695	17.3	394	15.3	13.9-16.7	203	15.5	13.5-17.4	191	15.1	13.1-17.1
Exclusive breastfeeding											
≥4 months	3,116	79.5	2,079	81.2	79.7-82.7	1,036	79.4	77.2-81.6	1,043	83.0	81.0-85.1
Maternal smoking											
yes	563	13.8	329	12.6	11.3-13.9	171	12.9	11.1-14.7	158	12.4	10.5-14.2
Young mother											
<25 years	319	7.8	198	7.6	6.6-8.6	117	8.8	7.3-10.3	81	6.3	5.0-7.7

*Doctor's diagnosis of asthma and/or hay fever in combination with allergy to furred pets and/or pollen and/or doctor's diagnosis of eczema at enrollment

^Mother smoked at least one cigarette per day during pregnancy and at the time of enrollment