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TITLE PAGE

Title: Development and comorbidity of eczema, asthma and rhinitis to age 12—data from the BAMSE birth cohort

Short title: Eczema, asthma and rhinitis during childhood

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ABSTRACT

Background: Allergy-related diseases are a public health issue but knowledge on development and comorbidity among children is scarce.

Objective: To study the development of eczema, asthma and rhinitis in relation to sex and parental allergy, in a population-based cohort, during childhood.

Methods: At 1, 2, 4, 8, and 12 years parental questionnaires were used to obtain data on allergy-related diseases. Complete data for all 5 follow-up occasions were available from 2,916 children. Odds ratios for the risk of any allergic disease in relation to heredity and sex were calculated using generalized estimating equations.

Results: At 12 years 58% of the children had had eczema, asthma and/or rhinitis at some time. Disease turnover was high for all three diseases throughout the study. Comorbidity increased with age and at 12 years 7.5% of all the children were affected by at least two allergy-related diseases. Parental allergy was associated with increased comorbidity and more persistent disease, and increased the risk of having any allergy-related disease (adjusted OR 1.76; 95% CI 1.57-1.97) up to 12 years. Male sex was associated with an increased risk throughout childhood. Boys and girls did not differ in disease persistence, and for comorbidity the differences were minor.

Conclusions: Allergy-related diseases may affect a majority of children. Eczema, asthma and rhinitis develop dynamically throughout childhood and allergic comorbidity is common. These findings indicate that allergy-related diseases should neither be seen nor studied as isolated entities.

INTRODUCTION

Allergy-related diseases have become a public health issue. In order to improve disease management we need to understand the development and comorbidity of eczema, asthma and rhinitis. Data indicate that allergic morbidity in childhood, though transient, is of importance for allergy-related diseases in adulthood.(1-5) Comorbidity between eczema, asthma and rhinitis has mainly been studied in selected or high risk cohorts of children,(6-12) but such studies show that comorbidity is substantial and associated with persistence and severity(13-15).

However, we still know little about the development and comorbidity of allergy-related diseases over time in a general paediatric population.(16) To our knowledge no study has yet investigated the dynamics of changes in eczema, asthma and rhinitis combined, from birth until adolescence, and related them to sex and parental allergy. The purpose of this prospective study was to investigate the development of eczema, asthma and rhinitis from birth up to 12 years of age with a particular focus on comorbidity and disease persistence in relation to sex and parental allergy in a population-based birth cohort.

MATERIAL AND METHODS

Study subjects

The BAMSE project is a longitudinal population-based cohort in which children were included at birth and prospectively followed during childhood. In brief, parents of all children born between 1994 and 1996 living in predefined areas of Stockholm County were asked to participate.(17) The BAMSE cohort comprised 4,089 infants, corresponding to 75% of the eligible subjects. Detailed data on residential characteristics, environmental factors and

parental allergy were obtained when the infant was two months old from a baseline parental questionnaire.(17) When the child was 1, 2, 4, 8 and 12 years, the parents completed questionnaires focusing on symptoms of eczema, asthma and rhinitis during the previous 12 months. To prevent symptoms from being counted twice the questions at age 1 year asked for symptoms up to 1 year of age and at age 2 years for symptoms between 1 and 2 years of age. Complete data on all health outcomes at every follow-up were available for 2,916 children (71% of the original cohort). These children were included in the present study so that complete analyses of disease onset, persistence and remission could be performed.

Definition of background variables

Previously identified background variables for the development of allergy-related diseases were used in the present analyses. With the exception of duration of breastfeeding, which was asked for at one year of age, all variables were based on information from the baseline questionnaire:

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.(18)

Young mother: maternal age ≤ 25 years at birth of the child.(19)

Low socioeconomic status: both parents blue collar workers according to the Nordic standard occupational classification and Swedish socio-economic classification.(20)

Tobacco exposure: mother smoked at least one cigarette per day during pregnancy or at the time of enrolment.(21)

Exclusive breastfeeding during the first four months of life: children breastfed without exposure to formula or solid foods.(22)

Definition of allergy-related disease outcomes

Assessment of current allergy-related diseases was based on the follow-up questionnaires at age 1, 2, 4, 8, and 12 years:

Eczema: dry skin, itchy rashes with age-specific location for two weeks or more, and/or doctor's diagnosis of eczema in the past 12 months.(23) At age four only data on doctor's diagnosis in the past 24 months were available. To obtain 12-month prevalence rates only those reporting itchy rashes with age-specific location for two weeks or more, or use of topical corticosteroids in the past 12 months in combination with doctor's diagnosis of eczema in the past 24 months were included in the analysis.

Asthma – at age 1 and 2 years: at least three episodes of wheeze in combination with inhaled corticosteroids and/or signs of bronchial hyperreactivity without concurrent upper respiratory infection the year before follow-up. (24) Asthma – at age 4, 8, and 12 years: at least four episodes of wheeze in the past 12 months or at least one episode of wheeze in combination with occasional or regular use of prescribed inhaled corticosteroids.(18)

Rhinitis – at age 1 and 2 years: prolonged rhinitis symptoms two months or more in the past 12 months. Rhinitis at age 4, 8, and 12 years: prolonged rhinitis without common cold in the past 12 months.(25)

Comorbidity: having at least two of the diseases eczema, asthma or rhinitis at the same follow-up.

New cases: onset of an allergy-related disease which had not been present at any previous follow-up.

Total remission: never having a specific allergy related disease again that had been present at the previous follow-up.

Remission and relapse: not having a specific allergy-related disease that had been present at the previous follow-up and that will be present at one or more future follow-ups.

Statistics

The prevalence of allergy-related disease was assessed during a 12-month period and expressed in percent of total number of observations available. 95% confidence intervals (95% CI) were calculated and intervals that did not overlap were considered statistically significant. χ^2-tests were used for dichotomous variables. For evaluation of differences in disease persistence between groups, Wilcoxon Rank Sum test was used. The proportion of remission between each follow-up was calculated by dividing the number of remitting cases by the total number of children who had the disease at that same time point. The mean value for onset for each disease was calculated as the mean of the proportions of new cases at age 2, 4, 8 and 12 years. The mean value for remission for each disease was calculated as the mean of the proportions of remitting cases at age 1, 2, 4 and 8 years. Generalized estimated equations (GEEs)(26) with an unstructured correlation matrix were used to assess the impact of parental allergy and sex on development of any allergy-related disease over time. The model incorporated an interaction between time and exposure to evaluate the

effect of exposure over time. All statistical analyses were performed with STATA Statistical Software (release 11.1; StataCorp, College Station, Texas, USA).

RESULTS

Representativeness of the study samples

There were no differences between children in the study population (n=2,916) and those in the study base (n=4,089) with regard to previously identified risk factors for development of allergy related diseases (Table S1). This also held true for the prevalence of eczema, asthma and rhinitis, although the rates tended to be somewhat lower for those participating at each follow-up (Table S2).

Prevalence rates of allergy-related diseases

Figure 1 shows the 12-month period prevalence rates for eczema, asthma and rhinitis as well as of any of these diseases at age 1, 2, 4, 8, and 12. At 12 years of age, 1,695 children (58%) had had at least one of these allergy-related diseases at some time. The prevalence of eczema peaked between 2 and 4 years of age, whereas rhinitis continued to increase in prevalence with increasing age. Between 4 and 12 years the asthma prevalence was rather stable. Twenty-two percent (629 of 2,916) of all children had had one disease at one follow up only, while 36% (1,066 of 2,916) either had one disease at more than one follow-up, or two or more of the diseases eczema, asthma and rhinitis during the study period. Among children with parental allergy, 66% (858 of 1,291) had an allergy-related disease before 12

years of age, compared to 52% (837 of 1,625) of children with no parental allergy, p<0.001 (Fig S1). Notably, children with parental allergy, irrespective of age, had significantly higher prevalence of all of the allergy-related diseases studied (all p<0.039) with the exception of asthma (p=0.200) and rhinitis (p=0.058) at one year of age. After adjustment for known confounders the overall impact of having parental allergy on development of any of the diseases eczema, asthma and rhinitis up to 12 years was of 1.76 (95% CI, 1.57-1.97). The impact of parental allergy on allergy-related disease development tended to increase with age of the study subjects, figure 2. Male sex was associated with an increased risk (adjusted OR 1.19, 95% CI 1.06-1.33) for development of any allergy-related disease up to 12 years and this association was rather stable over time, figure 2. Boys had a lifetime prevalence of any allergy related disease of 60% (892 of 1,488) and the corresponding figure for girls was 56% (803 of 1,428), p=0.042. This difference was mainly explained by higher prevalence rates of asthma and rhinitis among boys.

Disease turnover and persistence

Disease turnover, evaluated as onset and remission is illustrated in figure 3. The average proportion of new cases of the diseases studied at all observation time points was 53% and the corresponding proportion for total remission was 44%. The numbers of new cases, remitting cases with subsequent relapse and cases in total remission at all ages, are presented in table 1. Figure 3 also shows the proportion of children with eczema, asthma or rhinitis who had the disease at one, two or three or more follow-up occasions before 12 years of age. Since eczema often debuts early in life, it appeared more persistent than

asthma and rhinitis. However, from 4 to 12 years of age, disease persistence was almost the same for eczema, asthma and rhinitis (data not shown). The pattern of onset and remission for eczema, asthma and rhinitis was similar among children with and without parental allergy, as well as among boys and girls, even though onset of eczema at 2 years was more common among girls (data not shown). Children with parental allergy had more persistent eczema, asthma and rhinitis than children without parental allergy, all $p<0.001$. Boys and girls did not differ in terms of disease persistence.

Comorbidity of eczema, asthma and rhinitis

The overlap between eczema, asthma and rhinitis at the different follow-ups is illustrated in figure 4. Comorbidity became more prevalent with age. At least two allergy related diseases were found in 1.8% of the children at 1 year of age. At 2, 4, 8, and 12 years the corresponding proportions were 2.3%, 5.9%, 5.5%, and 7.5%. Among children who had an allergy related disease, allergic comorbidity was more prevalent among those with parental allergy. However, differences in comorbidity between boys and girls were minor (Table 2).

Asthma did not occur in isolation as often as eczema or rhinitis. Thus, asthma was associated with eczema and/or rhinitis in 38% at 1 year and in 67% at 12 years. This is to be compared with 42% of children with eczema and 33% of children with rhinitis having any additional allergy-related disease at age 12.

DISCUSSION

This study of a large unselected population-based birth cohort provides new insights regarding the development and comorbidity of allergy-related diseases in children. We found that by the age of 12 years, two out of three children with and every second child without parental allergy had had eczema, asthma and/or rhinitis. Furthermore, disease turnover was substantial with many new and remitting cases throughout the study period. Comorbidity increased from 1.8% at 1 year to 7.5% at 12 years in the study population and was more prevalent among children with parental allergy. Sex did not seem to influence disease persistence. Asthma was more often associated with eczema and/or rhinitis than eczema or rhinitis was associated with any of the other allergy-related diseases.

The strengths of this study are the prospective design and the large number of participants with complete data up to 12 years of age, which is unique. Moreover, assessment of eczema, asthma and rhinitis, on five occasions during the first 12 years of life reduces the risk of recall bias. The prevalence rates for eczema and rhinitis in our study agreed well with other population-based studies of similar age groups.(13, 27, 28) However, the asthma prevalence tended to be lower than that found by others(29-32), which may be explained by our strict definition. The overall prevalence rates found in our study are comparable to the Isle of Wight birth cohort study, in which 40% of the children had had an allergy-related disease at some time before reaching 4 years of age.(16) In our study the corresponding proportion was 45%.

One concern about our results is whether the prevalence rates might be overestimated. Since the BAMSE birth cohort study was designed to investigate allergy-related diseases it is possible that families with children who have allergic symptoms would be more prone to participate. However, as shown in table 2, loss to follow-up was more common among children with allergy-related diseases, a phenomenon also reported by others (33). With this in mind, it is noteworthy that more than half of the children in our study had eczema, asthma and/or rhinitis before adolescence, even if parental allergy was not present.

Comparison with other studies

It is well known that prevalence rates of allergy-related diseases differ between boys and girls and between families with and without allergic disease. However, reports on the influence of sex and parental allergy on allergic comorbidity are scarce. No obvious differences between boys and girls could be found in the German MAS study when rhinitis and concomitant wheeze were evaluated.(34) In our study, sex did not influence the persistence of any of the conditions studied. Disease turnover was only slightly affected by sex, with onset of eczema being more common among girls 2 years old. Similarly, the Isle of Wight study found no sex differences in disease turnover up to 10 years of age among children with eczema. However, from 10 to 18 years remission was more common among boys.(28) Onset and remission of asthma did not differ between boys and girls in our study, in congruence with some, but not all previous reports. In a recent study of remission and disease persistence among children 5-12 years with asthma, no influence of sex could be demonstrated.(35) However, in a selected cohort of children with doctor's diagnosis of

asthma before 6 years of age and followed up to 12 years, asthma was more persistent in boys than in girls.(36) Furthermore, it has recently been shown that sex differences in prevalence rates of asthma among teenagers may partly be explained by higher remission of asthma among boys.(37) These apparently contradictory results might be explained by differences in study design and selection of subjects, but also by age differences among the children in the different studies. This underlines the need for population-based cohorts followed over a long time.

Asthma seems to present as a single disease in less than half of the cases after 4 years of age and a probable explanation could be that the asthma definition we used does not include milder cases. However, another study showed that 56% of 5-year-old children with wheeze had concomitant eczema and/or rhinoconjunctivitis.(38) This knowledge may be of importance when studying phenotypes of allergy-related diseases in relation to early life events. The large number of new and remitting cases at all ages found in our study raises the question of when an outcome should be evaluated – and over how long a time period – in studies addressing risk factors for disease development in childhood.

Conclusions

We found that allergy-related diseases affect a majority of the paediatric population during the first 12 years of life and that the development of eczema, asthma and rhinitis is a dynamic process: both new cases and remission are common throughout childhood. These findings call for further research to identify phenotypes on the basis of comorbidity and disease development that are associated with subsequent disease.

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Contributors: MW and GP initiated the BAMSE cohort. IK and EH coordinated the data collection. NB, MW, IK, GP, AB, GL, EM, CA and EÖ designed the current study. NB, AB, TL 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 statement: All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and claim no conflict of interest related to the submitted work.

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

Supportive information:

Figure S1. Prevalence rates of allergy-related diseases up to 12 years in children with and without parental allergy in the BAMSE birth cohort.

Table S1. Distribution of risk factors for allergy-related diseases in the study population compared to the study base.

Table S2. Twelve-month prevalence rates of allergy-related diseases in the study population compared to the study base.

Tables

Table S1 Distribution of risk factors for allergy-related diseases in the study population compared to the study base

Variable*	**Study base**			**Study population**		
Data collected at enrolment	N=4,089 (100%)			n=2,916 (71.3%)		
	n	%	95% CI	n	%	95% CI
Sex						
Male	2065/4089	50.5	49.0–52.0	1488/2916	51.0	49.2–52.8
Parental allergy**						
any or both	1746/4045	43.2	41.6–44.7	1291/2916	44.3	42.5–46.1
Maternal age						
< 25 years	319/4088	7.8	7.0–8.6	196/2915	6.7	5.8–7.6
Socioeconomic status						
blue collar workers	695/4018	17.3	16.1–18.5	431/2882	15.0	13.7–16.3
Maternal tobacco smoking***						
Yes	563/4086	13.8	12.7–14.8	346/2916	11.9	10.7–13.0
Data collected at 1 year	n=3,925 (96%)			n=2,916 (71.3%)		
	n	%	95% CI	n	%	95% CI
Breastfeeding exclusive ≥4 months						
No	803/3919	20.5	19.2–21.8	543/2912	18.7	17.2–20.1

*Internal missing 0–1.7%

**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 enrolment

***Mother smoked at least one cigarette per day during pregnancy and at the time of enrolment

Table S2 Twelve-month prevalence rates of allergy-related diseases in the study population compared to the study base

Variable	study base			study population		
1 year	**n**	**%**	**95% CI**	**n**	**%**	**95% CI**
Eczema	594/3923	15.1	14.0–16.3	440/2916	15.1	13.8–16.4
Asthma	151/3924	3.9	3.2–4.5	101/2916	3.5	2.8–4.1
Rhinitis	145/3920	3.7	3.1–4.3	103/2916	3.5	3.1–4.3
2 years	**n**	**%**	**95% CI**	**n**	**%**	**95% CI**
Eczema	730/3839	19.0	17.8–20.3	542/2916	18.6	17.2–20.0
Asthma	219/3835	5.7	5.0–6.4	157/2916	5.4	4.6–6.2
Rhinitis	154/3840	4.0	3.4–4.6	112/2916	3.8	3.1–4.5
4 years	**N**	**%**	**95% CI**	**n**	**%**	**95% CI**
Eczema	729/3721	19.6	18.3–20.9	546/2916	18.7	17.3–20.1
Asthma	260/3704	7.0	6.2–7.8	182/2916	6.2	5.4–7.1
Rhinitis	413/3685	11.2	10.2–12.2	314/2916	10.8	9.6–11.9
8 years	**N**	**%**	**95% CI**	**n**	**%**	**95% CI**
Eczema	428/3397	12.6	11.5–13.7	355/2916	12.2	11.0–13.4
Asthma	215/3397	6.3	5.5–7.1	177/2916	6.1	5.2–6.9
Rhinitis	462/3409	13.6	12.4–14.7	380/2916	13.0	11.8–14.3
12 years	**N**	**%**	**95% CI**	**n**	**%**	**95% CI**
Eczema	399/3353	11.9	10.8–13.0	339/2916	11.6	10.5–12.8
Asthma	221/3339	6.6	5.8–7.5	189/2916	6.5	5.6–7.4
Rhinitis	693/3337	20.8	19.4–22.1	601/2916	20.6	19.1–22.1

Table 1 New and remitting cases from 1 to 12 years for eczema, asthma and rhinitis in the BAMSE birth cohort

Eczema

	all cases	**new cases**		**total remission**		**remission & relapse**	
age (yrs)	n	n	%	n	%	n	%
1	440	440	na	118	26.8	65	14.8
2	542	285	52.6	164	30.3	65	12.0
4	546	191	35.0	267	48.9	63	11.5
8	355	90	25.4	212	59.7	na	
12	339	94	27.7	na			

Asthma

	all cases	**new cases**		**total remission**		**remission & relapse**	
age (yrs)	n	n	%	n	%	n	%
1	101	101	na	34	33.7	13	12.9
2	157	103	65.6	66	42.0	18	11.5
4	182	102	56.0	90	49.5	15	8.2
8	177	87	49.2	97	54.8	na	
12	189	83	43.9	na			

Rhinitis

	all cases	**new cases**		**total remission**		**remission & relapse**	
age (yrs)	n	n	%	n	%	n	%
1	103	103	na	48	46.6	33	32.0
2	112	90	80.4	60	53.6	32	28.6
4	314	279	88.9	131	41.2	58	18.5
8	380	225	59.2	144	37.9	na	
12	601	287	47.8	na			

New cases are defined as onset of an allergy-related disease which had not been present at any previous observational point. Total remission is defined as never having a specific allergy related disease again that had been present at the previous follow-up. Remission & relapse is defined as not having a specific allergy-related disease that had been present at the previous follow-up and that will be present at one or more future follow-ups.

na = not applicable

Table 2 Comorbidity* among children 1 to 12 years with allergy-related disease in the BAMSE birth cohort according to sex and parental allergy

	parental allergy (n=1,291)			no parental allergy (n=1,625)		
age(yrs)	**n**	**%**	**95% CI**	**n**	**%**	**95% CI**
1	33/315	10.5	7.1–13.9	20/270	7.4	4.3–10.6
2	38/395	9.6	6.7–12.5	28/338	8.3	5.3–11.2
4	115/455	**25.3**	**21.3–29.3**	56/398	**14.1**	**10.6–17.5**
8	108/408	**26.5**	**22.2–30.8**	48/318	**15.1**	**11.1–19.1**
12	139/484	**28.7**	**24.7–32.8**	79/397	**19.9**	**16.0–23.8**

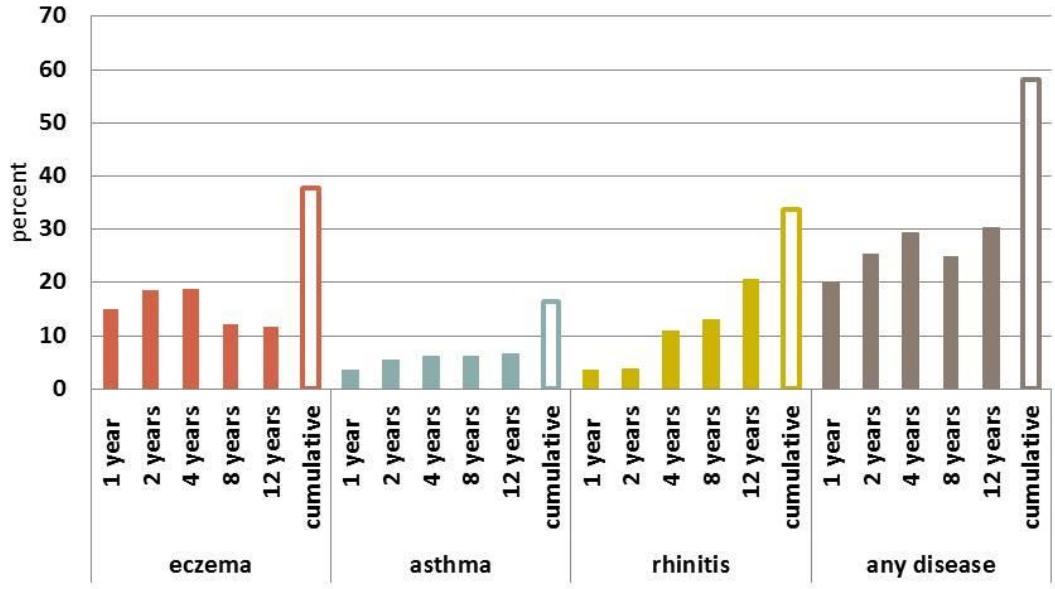
	boys (n=1,488)			girls (n=1,428)		
age(yrs)	**n**	**%**	**95% CI**	**n**	**%**	**95% CI**
1	37/321	11.5	8.0–15.0	16/264	6.1	3.2–9.0
2	38/399	9.5	6.6–12.4	28/334	8.4	5.4–11.4
4	110/454	**24.2**	**20.3–28.2**	61/399	**15.3**	**11.7–18.8**
8	81/397	20.4	16.4–24.4	75/329	22.8	18.2–27.4
12	119/470	25.3	21.4–29.3	99/411	24.1	19.9–28.2

*Comorbidity is defined as having two or three of the diseases eczema, asthma and rhinitis at the same follow-up. Statistically significant differences are written in bold.

Figures

Figure 1

Prevalence rates of allergy related diseases up to 12 years in the BAMSE birth cohort n=2,916

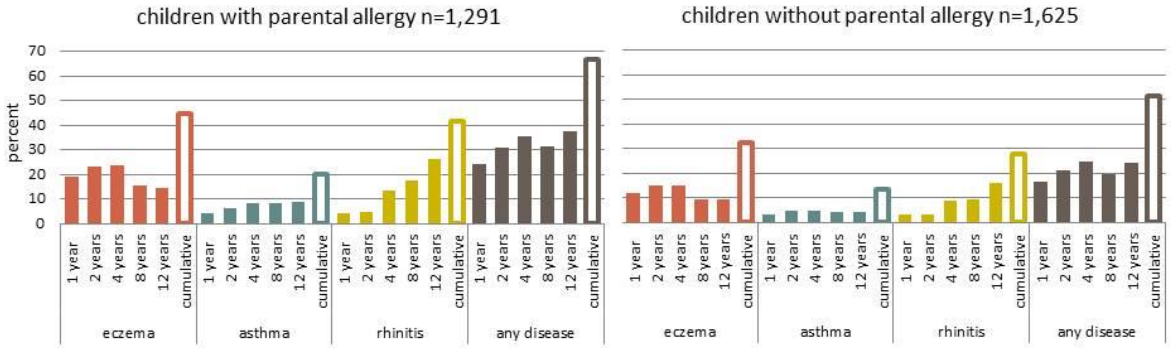


Footnote:

12-month prevalence of eczema, asthma, rhinitis and any symptom at age 1, 2, 4, 8, and 12 years. Empty bars show the cumulative prevalence at 12 years (n=2,916)

Figure S1

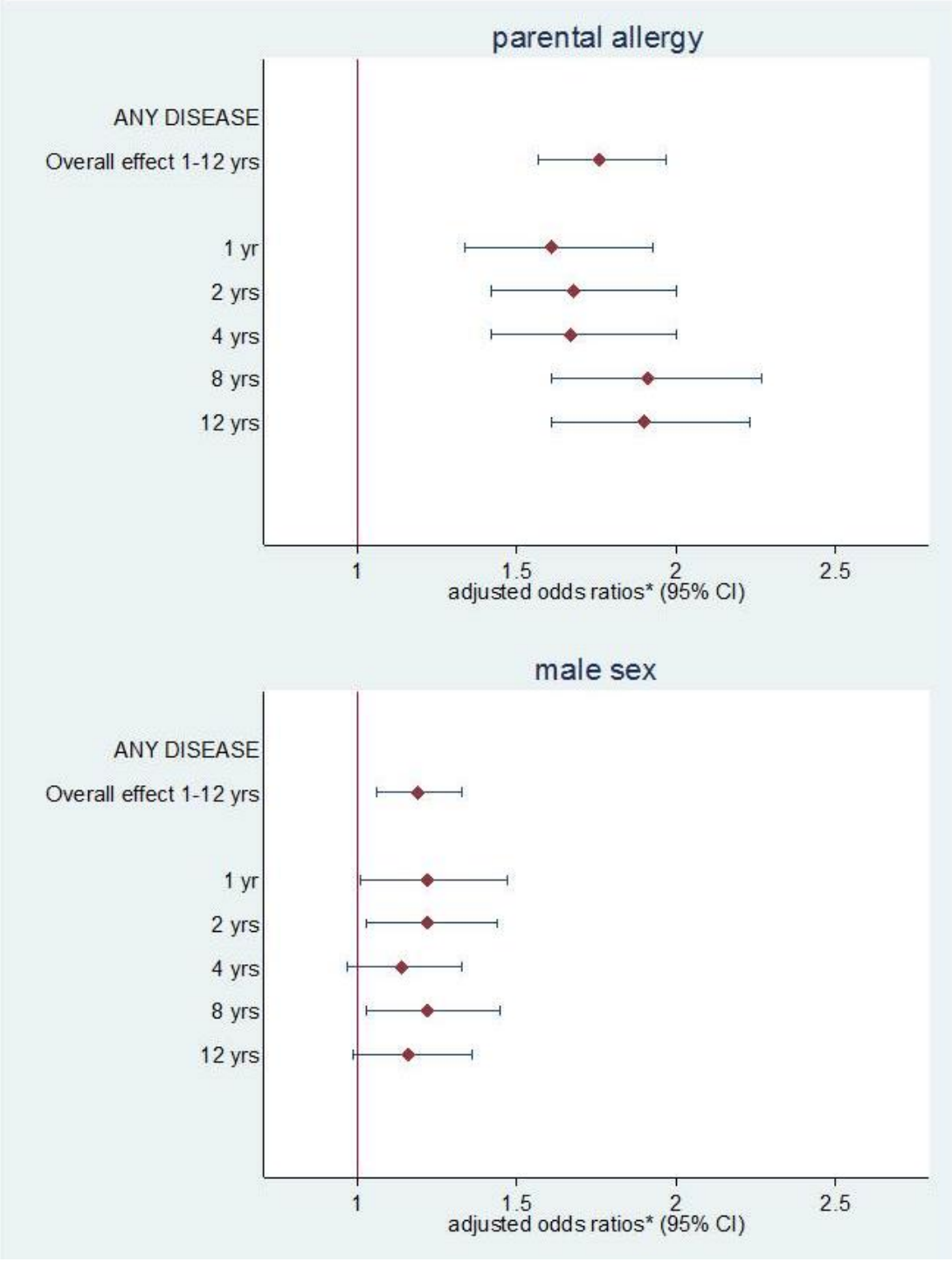
Prevalence rates of allergy related diseases up to 12 years in children with and without parental allergy in the BAMSE birth cohort



Footnote:

12-month prevalence of eczema, asthma, rhinitis and any symptom at age 1, 2, 4, 8, and 12 years in children with and without parental allergy. Empty bars show the cumulative prevalence at 12 years.

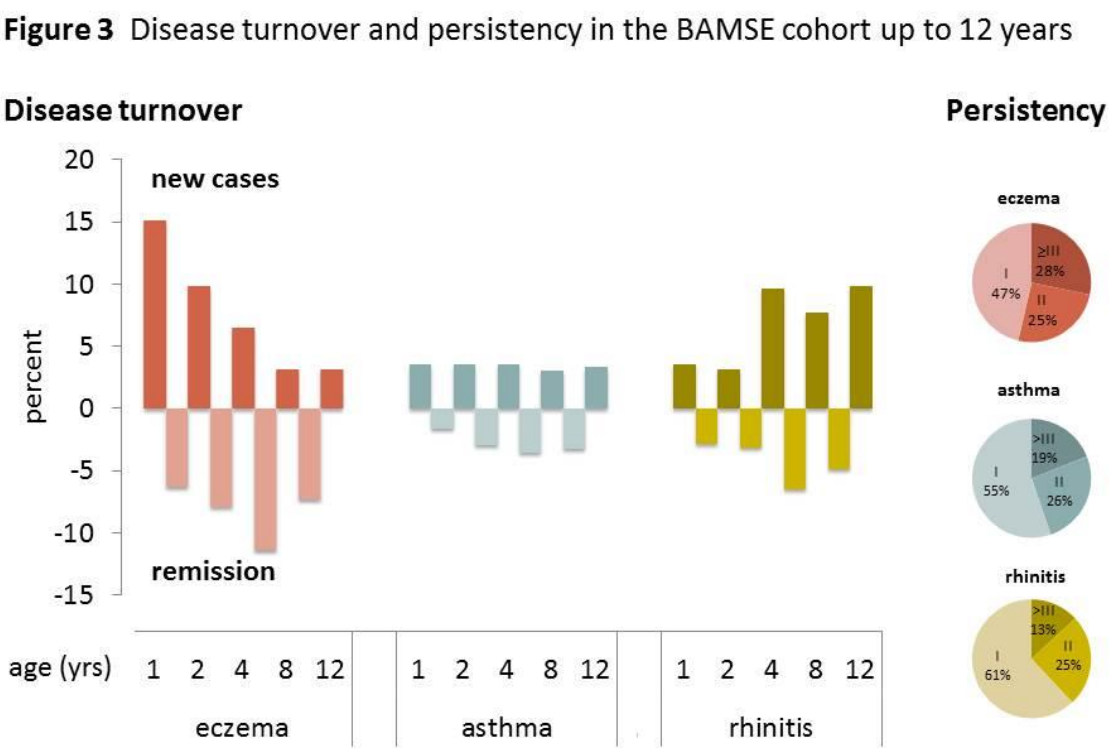
Figure 2 Parental allergy and sex in relation to development of any allergy-related disease† up to 12 years in the BAMSE cohort



Footnote:
†eczema and/or asthma and/or rhinitis * ORs and 95% CIs were calculated by using GEEs, adjusted for the confounders: exclusive breastfeeding <4 months, maternal smoking, low socioeconomic status and young mother (≤ 26 years) n=2.916

Figure 3

Disease turnover and persistence up to 12 years of age in the BAMSE birth cohort



Footnote:

Turnover indicates the percentage in the population (n=2,916) of new and remitting cases at each observation point. New cases were defined as onset of disease which had not been present at any previous observation point and remission was defined as not having a disease that had been present at the previous observation point. Persistence indicates the proportion of children who had a disease at one, two or three or more observation points among the children who had ever had the same disease.

Figure 4

Comorbidity of eczema, asthma and rhinitis up to 12 years in the BAMSE birth cohort

Figure 4

Comorbidity of eczema, asthma and rhinitis up to 12 years in the BAMSE birth cohort n=2,916

	1 year		2 years		4 years		8 years		12 years	
	n	%	n	%	n	%	n	%	n	%
eczema only	397	14	487	17	403	14	245	8	196	7
asthma only	63	2	106	4	105	4	81	3	63	2
rhinitis only	72	2	74	3	174	6	244	8	404	14
eczema and asthma	22	1	32	1	31	1	20	1	21	1
eczema and rhinitis	15	1	19	1	94	3	60	2	92	3
asthma and rhinitis	10	0	15	1	28	1	46	2	75	3
eczema, asthma and rhinitis	6	0	4	0	18	1	30	1	30	1
no disease (not shown in figure)	2331	80	2179	75	2063	71	2190	75	2035	70

Footnote:

Venn diagrams showing comorbidity between eczema, asthma and rhinitis at age 1, 2, 4, 8, and 12 years.

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