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Early-life sensitization to hen's egg predicts asthma and rhinoconjunctivitis at 14 years of age

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Abstract

Background: Sensitization to both inhalant and food allergens has been shown to be risk factors for development of asthma and rhinoconjunctivitis (RC). However, few studies have addressed the role of transient or persistent IgE sensitization to specific allergens in early life for later development of allergic diseases. The aim of this study was to explore the association between transient and persistent sensitization in early-life and the development of asthma and RC at 6 and 14 years.

Methods: The DARC cohort is a prospective non-interventional birth cohort study comprising 562 children. For the purpose of this study, we examined a subgroup of the original cohort with specific IgE measured at, at least 3 of 4 follow-ups between 3 and 18 months of age (n=366). Multiple logistic regression models were used to investigate the association between transient and persistent early-life sensitization to groups of and to individual allergens and asthma and RC at 6 and 14 years compared to a reference group with no sensitization.

Results: Both transient and persistent early-life sensitization to cow's milk or hen's egg proteins were associated with asthma (aOR 3.99(1.41-11.32) and 5.95(1.78-19.92)) and RC (aOR 2.94(1.19-7.28) and 6.18(1.86-20.53)) at 14 years, this association being driven mainly by sensitization to hen's egg. Transient early-life sensitization to HDM had increased risk of asthma (aOR 3.80(1.17-12.41)) at 14 years.

Conclusions: Early transient and persistent IgE sensitization to hen's egg was associated with asthma and RC at 14 years. Furthermore, sensitization to HDM was associated with asthma at 14 years.

Keywords: Asthma, Rhinoconjunctivitis, sensitization, transient, persistent, childhood, predictors, birth cohort

Introduction

Atopic diseases are among the most common chronic diseases in children and adolescents representing a substantial health and socioeconomic burden. Sensitization has been shown to precede the development of atopic disease (1-6) and early sensitization to both inhalant and food allergens has in some studies been shown to increase the risk for the development of asthma (1-6) and rhinoconjunctivitis (7-9) later in childhood. The association between IgE sensitization and allergic diseases has been studied intensively, but only few studies have addressed the role of both transient and persistent early-life sensitization to specific allergens (1) for later development of allergic diseases finding persistent sensitization to food allergens important. This indicates that early-life sensitization might be a predictor for later development of allergic airway diseases.

The prospective design of The Danish Allergy Research Center (DARC) cohort with frequent clinical follow-ups including measurements of specific IgE offers a unique opportunity to investigate the role of early sensitization to specific allergens. The aim of this study was to explore the association between transient and persistent sensitization to groups of allergens as well as individual allergens in early-life and the development of asthma and rhinoconjunctivitis at 6 and 14 years of age.

Methods

The DARC cohort is an unselected, prospective non-interventional birth cohort study comprising 562 of 1095 consecutive full-term children born the first two weeks of each month at Odense University Hospital, Denmark from November 1998 to November 1999. The children were evaluated during the first month of life and follow-up investigations were performed at 3, 6, 12, 18 months and 3, 6 and 14 years of age. All visits included questionnaire-based interviews by a doctor, clinical examination and specific IgE (s-IgE) measurements. A detailed description was published previously (10-12).

Study population: Of the original cohort of 562 children, subjects with at least 3 measurements of specific IgE at follow-ups at 3, 6, 12 and 18 months of age, were chosen for further analysis (n=366).

Diagnostic criteria: Asthma was diagnosed if one of the following criteria were fulfilled: (i) recurrence of at least two of three symptoms: cough, wheeze and shortness of breath within the previous 12 months not triggered only by an infection (ii) doctor's diagnosis of asthma prior to follow-up visit plus ongoing treatment, (iii) symptoms suggesting asthma within the previous 12 months plus a positive reversibility test (spirometry) to inhaled β2-agonist or corticosteroid.

Rhinoconjunctivitis (RC) was diagnosed in participants with at least two separate episodes of one or more symptoms of: sneezing, runny or blocked nose or itchy, red and watery eyes in the previous 12 months apart from upper airway infections.

Early sensitization: Sensitization up to and including 18 months of age.

Specific IgE at 3, 6, 12 and 18 months was measured by Magic Lite (ALK-ABELLÓ, Hørsholm, Denmark) and sensitization was defined as s-IgE ≥ 1.43 SU/ml to the allergens grass, birch, cat, dog, dermatophagoides pteronyssinus, dermatophagoides farina , cladosporium herbarum and alternaria alternata, hen's egg (egg), cow's milk (milk), wheat, codfish and peanut.

'*Transient sensitization'* was defined as sensitization to the allergen(s) of interest at one or two study visits between and inclusive 3 and 18 months of age (if two, not consecutive).
'*Persistent sensitization*' was defined as sensitization to the allergen(s) of interest at two or more consecutive study visits.
'*Other sensitization*' was defined as having s-IgE≥1.43 SU/ml to other allergens than the allergens of interest.
'*No sensitization*' was defined as having s-IgE < 1.43 SU/ml to all the allergens mentioned above.

Statistics: Results are given as prevalence with 95% confidence interval (95%CI). Two sample comparison test (The Pearson χ^2 test) of baseline characteristics was used to assess potential differences between the study population (n=366) and those that were not included (n=196).
Multiple logistic regression models were used to investigate the association between different categories of early sensitization and asthma or rhinoconjunctivitis (RC) at 6 or 14 years.
We created 4 categories of sensitization: not sensitized to any allergen (reference group), transient sensitized to the allergens of interest (transient), persistent sensitized to the allergens of interest (persistent) and a group not sensitized to the group of allergens of interest but sensitized to one or more other allergens (other sensitization).
To gain power in the analysis we created groups of allergens; milk/egg, grass/birch, cat/dog (pets), dermatophagoides pteronyssinus, dermatophagoides farina (House Dust Mites (HDM)).
Based on current literature, confounders were identified by a priori knowledge of their association with sensitization and atopic airway diseases: Gender (2, 7, 13), parental atopy (14), early atopic dermatitis (4), and early food allergy (7, 15). These confounders were

included in the multiple logistic regression models directly without further analysis. Other possible confounders; maternal smoking during pregnancy, environmental tobacco smoke before 2 years of age (ETS), breastfeeding, parental social class, early wheeze, having pets and having siblings were not included directly. Those confounders remained in the final model only if they resulted in a change of 10% or more in the odds ratio of the relevant sensitization category.
Using Spearman's correlation coefficients negligible correlation was found ($r \leq 0.3$) between the latter confounders, except for the correlation between maternal smoke in pregnancy and (ETS) which was moderate ($r=0.34$). Therefore, all these variables were retained for further analysis.

Adjusted effect estimates were given as adjusted odds ratio (aOR) with 95% confidence interval (95%CI). Statistical analyses were performed using STATA/SE (Stata Corporation, College Station, TX, USA). P-values less than 0.05 were considered significant.

Missing date were checked manually and found not to influence the result.

Ethics: The study was conducted according to the latest version of the Declaration of Helsinki for biomedical research involving humans and approved by the Regional Scientific Ethical Committee for Southern Denmark: DARC cohort (S-VF-19980101).

Results

A total of 366 children were tested with specific IgE measurements at, at least 3 of 4 visits between 3 and 18 months of age and 308 of these participated at 6 years (84%) and 284 at 14 years (78%), (Figure 1). As shown in Table 1, there was only minor baseline discrepancies between those included and those excluded from the analysis.

Table 1a: Background characteristics for the study population and those not included.

	Study population	Not included
At birth	N=366	N=196
Boys	182 (49.7%)	103 (52.6%)
Girls	184 (50.3%)	93 (47.5%)
Maternal predisposition	102 (27.9%)	55 (28.1%)
Paternal predisposition	106 (29.0%)	46 (23.5%)
Parental predisposition	37 (10.1%)	11 (5.6%)
Social class 1-2	127 (34.7%)*	46 (23.5%)*
Social class 3-4	167 (45.6%)	81 (41.3%)
Social class 5	72 (19.7%)*	69 (35.2%)*
Maternal smoking during pregnancy	103 (28.3%)*	80 (40.8%)*
Maternal smoke at inclusion	45 (12.3%)*	51 (26.0%)*
Paternal smoke at inclusion	71 (19.4%)	50 (25.7%)

*indicates statistical significant differences ($p<0.05$) using Pearson χ^2 test.

Table 1b: Comparison of the prevalence of atopic diseases at 3 years in the study population and those not included. Only those attending the 3 years follow-up are included.

Diagnosis at 3 years	Study population n=320	Not included n=91
Atopic dermatitis	58 (18.1%)	11 (12.1%)
Asthma	49 (15.3%)	17 (18.7%)
Rhinoconjunctivitis	26 (8.1%)	7 (7.7%)

The prevalence of asthma and RC in the study population was 6.8% (4.2-10.2) and 14.6% (10.9-19.1) at 6 years and 14.8% (10.9-19.5) and 34.9% (22.3-40.7) at 14 years of age (Figure 1).

The majority of those with early-life sensitization to inhalant allergens were transiently sensitized in contrast to those with sensitization to food allergens where more than 50% were persistently sensitized at the 12 and 18 months follow-up visit (Figure 2).

Sensitization to any allergen between 3 and 18 months was seen in 46.5% (170/366), and 25.1% (94/366) of the children were sensitized to at least one of the following allergens: egg, milk, grass, birch, pets or HDM whereas 76 children were sensitized to other allergens; -especially to wheat (n=59).

No persistent sensitization to grass, birch and cat allergens were found (Table 2)Those with transient sensitization to grass/birch, cat/dog and HDM were associated with RC at 14 years in the crude but not in the adjusted analysis analysis (Table 2). Participants with either transient or persistent early sensitization to milk or egg compared to no early-life sensitization had increased risk of asthma and RC at 14 years, and this association was mainly driven by sensitization to hen's egg. Persistent early sensitization to egg was also a risk factor for asthma at 6 years (Table 3). Participants with transient early sensitization to HDM had increased risk of asthma at 14 years compared to those with no early-life sensitization (Table 3).

Table 2: Associations (crude Odds Ratio [cOR]) between transient and persistent sensitization to groups of allergens as well as individual allergens and asthma and rhinoconjunctivitis (RC) at 6 and 14 years of age. Results are derived from logistic regression models. Adjusted OR in bold indicates significant association in the logistic regression model ($p<0.05$)

		Asthma 6 yrs	RC 6 yrs	Asthma 14 yrs	RC 14 yrs
	No sensitization (n/N)	**8/159**	**19/159**	**17/149**	**40/149**
	aOR (reference group)	**1**	**1**	**1**	**1**
Egg/Milk	Transient sens. (n/N)	**5/29**	7/29	**9/26**	**14/26**
	cOR (95% CI)	**3.93 (1.19-13.02)**	2.35 (0.88-6.22)	**4.11 (1.59-10.66)**	**3.18 (1.36-7.45)**
	Persistent sens. (n/N)	**5/23**	**7/23**	**8/26**	**19/26**
	cOR (95% CI)	**5.24 (1.55-17.75)**	**3.22 (1.18-8.84)**	**3.45 (1.30-9.14)**	**7.40 (2.89-18.92)**
	Other sens. than milk/egg (n/N)	3/97	12/97	8/83	26/83
	cOR (95% CI)	0.60 (0.16-2.33)	1.04 (0.48-2.25)	0.83 (0.34-2.01)	1.24 (0.69-2.24)
Egg	Transient sens. (n/N)	3/19	**6/19**	**8/19**	**13/19**
	cOR (95% CI)	3.54 (0.85-14.69)	**3.40 (1.16-10.01)**	**5.65 (1.99-16.00)**	**5.90 (2.10-16.59)**
	Persistent sens. (n/N)	**5/23**	**7/23**	**7/25**	**18/25**
	cOR (95% CI)	**5.24 (1.55-17.75)**	**3.22 (1.18-8.84)**	**3.02 (1.10-8.28)**	**7.01 (2.72-18.03)**
	Other sens. than egg (n/N)	5/107	13/107	10/91	28/91
	cOR (95% CI)	0.93 (0.29-2.91)	1.02 (0.48-2.16)	0.96 (0.42 -2.20)	1.21 (0.68-2.15)
Milk	Transient sens. (n/N)	**3/14**	3/14	2/12	5/12
	cOR (95% CI)	**5.15 (1.19-22.19)**	2.01 (0.51-7.86)	1.55 (0.31-7.69)	1.95 (0.58-6.49)
	Persistent sens. (n/N)	**2/7**	2/7	**3/8**	**6/8**
	cOR (95% CI)	**7.55 (1.26-45.10)**	2.95 (0.53-16.27)	**4.66 (1.02-21.26)**	**8.18 (1.59-42.18)**
	Other sens. than milk (n/N)	8/128	21/128	20/115	**48/115**
	cOR (95% CI)	1.26 (0.46-3.45)	1.45 (0.74-2.83)	1.64 (0.81-3.29)	**1.95 (1.16-3.28)**
Grass/Birch	Transient sens. (n/N)	0/21	1/21	3/18	**10/18**
	cOR (95% CI)	NE	0.37 (0.05-2.90)	1.55 (0.41-5.92)	**3.41 (1.26 -9.24)**
	Persistent sens. (n/N)	0/0	0/0	0/0	0/0
	cOR (95% CI)	NE	NE	NE	NE
	Other sens. than grass/birch (n/N	13/128	25/128	22/117	**49/117**
	cOR (95% CI)	2.13 (0.86-5.32)	1.79 (0.94-3.42)	1.80 (0.91-3.57)	**1.96 (1.17-3.29)**
Cat/Dog	Transient sens. (n/N)	3/19	**7/19**	4/15	**9/15**
	cOR (95% CI)	3.54 (0.85-14.69)	**4.30 (1.51-12.26)**	2.82 (0.81-9.86)	**4.09 (1.37-12.21)**
	Persistent sens. (n/N)	0/3	0/3	1/3	2/3
	cOR (95% CI)	NE	NE	3.88 (0.33-45.13)	5.45 (0.48-61.76)
	Other sens. than cat/dog (n/N)	10/127	19/127	20/117	**48/117**
	cOR (95% CI)	1.61 (0.62-4.22)	1.30 (0.65-2.57)	1.60 (0.80-3.22)	**1.90 (1.13-3.18)**
HDM	Transient sens. (n/N)	2/20	4/20	**6/20**	**11/20**
	cOR (95% CI)	2.10 (0.41-10.65)	1.84 (0.56-6.09)	**3.33 (1.13-9.81)**	**3.33 (1.29-8.63)**
	Persistent sens. (n/N)	0/1	0/1	0/1	1/1
	cOR (95% CI)	NE	NE	NE	NE
	Other sens. than HDM (n/N)	11/128	22/128	19/114	**47/114**
	cOR (95% CI)	1.78 (0.69-4.55)	1.53 (0.79-2.97)	1.55 (0.77-3.14)	**1.91(1.14-3.22)**

ND: Not estimable

Table 3: Associations (adjusted Odds Ratio [aOR]) between transient and persistent sensitization to groups of allergens as well as individual allergens and asthma and rhinoconjunctivitis (RC) at 6 and 14 years of age. Results are derived from multiple logistic regression models and adjusted for relevant confounders. Adjusted OR in bold indicates significant association in the multiple logistic regression model (p<0.05)

		Asthma 6 years	RC 6 years	Asthma 14 years	RC 14 years
	No sensitization (n/N)	**8/159**	**19/159**	**17/149**	**40/149**
	aOR (reference group)	**1**	**1**	**1**	**1**
Egg/Milk	Transient sens. (n/N)	5/29	7/29	**9/26**	**14/26**
	aOR (95% CI)	2.61 (0.73-9.37)	1.42 (0.49-4.10)	**3.99 (1.41-11.32)**	**2.94 (1.19-7.28)**
	Persistent sens. (n/N)	**5/23**	7/23	**8/26**	**19/26**
	aOR (95% CI)	**4.84 (1.07-21.92)**	2.52 (0.68-9.42)	**5.95 (1.78-19.92)**	**6.18 (1.86-20.53)**
	Other sens. than milk/egg (n/N)	3/97	12/97	8/83	26/83
	aOR (95% CI)	0.60 (0.15-2.41)	1.15 (0.51-2.58)	0.76 (0.30-1.91)	1.30 (0.71-2.38)
Egg	Transient sens. (n/N)	3/19	6/19	**8/19**	**13/19**
	aOR (95% CI)	2.28 (0.49-10.51)	2.16 (0.66-7.04)	**5.52 (1.75-17.36)**	**5.44 (1.82-16.22)**
	Persistent sens. (n/N)	**5/23**	7/23	**7/25**	**18/25**
	aOR (95% CI)	**4.96 (1.08-22.89)**	2.59 (0.70-9.55)	**4.46 (1.32-15.08)**	**6.06 (1.84-19.92)**
	Other sens. than egg (n/N)	5/107	13/107	10/91	28/91
	aOR (95% CI)	0.96 (0.29-3.16)	1.05(0.48-2.30)	0.90 (0.38-2.14)	1.25 (0.69-2.26)
Milk	Transient sens. (n/N)	3/14	3/14	2/12	5/12
	aOR (95% CI)	3.72 (0.74-18.67)	1.01 (0.22-4.56)	1.66 (0.30-9.24)	1.34 (0.36-5.00)
	Persistent sens. (n/N)	2/7	2/7	**3/8**	6/8
	aOR (95% CI)	7.01 (0.76-64.82)	2.24 (0.28-18.07)	**8.90 (1.21-65.73)**	3.88 (0.58-26.15)
	Other sens. than milk (n/N)	8/128	21/128	20/115	**48/115**
	aOR (95% CI)	1.12 (0.39-3.22)	1.37 (0.67-2.80)	1.56 (0.75-3.26)	**1.86 (1.08-3.21)**
Grass/Birch	Transient sens. (n/N)	0/21	1/21	3/18	10/18
	aOR (95% CI)	NE	0.21(0.02-1.95)	1.49(0.36-6.05)	2.47 (0.84-7.27)
	Persistent sens. (n/N)	0/0	0/0	0/0	0/0
	aOR (95% CI)	NE	NE	NE	NE
	Other sens. than grass/birch (n/N)	13/128	25/128	22/117	**49/117**
	aOR (95% CI)	1.68 (0.63-4.49)	1.56 (0.77-3.15)	1.72 (0.84-3.55)	**1.81 (1.03-3.19)**
Cat/Dog	Transient sens. (n/N)	3/19	7/19	4/15	9/15
	aOR (95% CI)	1.88 (0.38-9.29)	1.67 (0.48-5.85)	2.71 (0.68-10.87)	1.88 (0.54-6.55)
	Persistent sens. (n/N)	0/3	0/3	1/3	2/3
	aOR (95% CI)	NE	NE	6.33 (0.39-103.55)	1.20 (0.08-18.43)
	Other sens. than cat/dog (n/N)	10/127	19/127	20/117	**48/117**
	aOR (95% CI)	1.50 (0.53-4.24)	1.28 (0.60-2.71)	1.61 (0.77-3.38)	**1.88 (1.06-3.33)**
HDM	Transient sens. (n/N)	2/20	4/20	**6/20**	11/20
	aOR (95% CI)	1.55 (0.25-7.60)	0.77 (0.17-3.48)	**3.80 (1.17-12.41)**	2.61 (0.92-7.43)
	Persistent sens. (n/N)	0/1	0/1	0/1	1/1
	aOR (95% CI)	NE	NE	NE	NE
	Other sens. than HDM (n/N)	11/128	22/128	19/114	47/114
	aOR (95% CI)	1.55 (0.56-4.28)	1.40 (0.67-2.93)	1.53 (0.73-3.24)	1.71 (0.97-3.00)

NE: Not estimable

Other sens.: Other sensitization was defined as having s-IgE≥1.43 SU/ml to other allergens than the allergens of interest.
Confounders: All categories were adjusted for: Gender, parental atopy, early atopic dermatitis and early food allergy. Further adjustments were made if there was a change of 10% or more in the odds ratio of the relevant sensitization category: Maternal smoking during pregnancy was included in the analysis of sensitization to egg/milk, egg, milk, pets and asthma. Early wheeze was included in the analysis of sensitization to pets, HDM (house dust mite) and asthma. Environmental tobacco smoke was included in the analysis of sensitization to grass/birch, pets and RC at 14 years. Breastfeeding was included in the analysis of sensitization to pets, HDM and RC.

Discussion

This study demonstrates that both persistent and transient early-life sensitization to hen's egg were associated with asthma and RC at 14 years, and persistent early sensitization to egg was associated with asthma at 6 years of age. Furthermore, early transient sensitization to HDM was associated with asthma at 14 years. We were unable to draw any conclusions on similar associations for the other groups of allergens, possibly due to the small number of positive s-IgE responses.

We have previously reported, that early-life sensitization to food allergens (egg and milk) was associated with asthma but not with RC at 6 years (2) and the same associations were found in the present study, although the chosen subgroup for analysis was different. The German MAS study (1) also found that persistent (at 1 and 2 years of age) sensitization to food allergens (egg, milk, soy and wheat) was associated with allergic asthma as well as rhinitis at 5 years. We found an association between early sensitization to egg or milk and RC at 6 years in the unadjusted analysis but not in the adjusted analysis.

Transient sensitization to allergens early in life can be considered a benign phenomenon with most children remaining asymptomatic (1, 16). However, persistent sensitization to allergens in early life has been associated with development of asthma later in childhood (1, 2). In this study we found that both transient and persistent early-life sensitization to egg allergens were associated with asthma and RC at 14 years (aOR=5.52, aOR=4.46 and aOR=5.44, aOR=6.06). The same conclusion of sensitization to egg allergens at 1 year and subsequent allergic asthma at 8 years was made in the Dutch PIAMA study (17). In the MACS study (18) no association between mono-sensitization to milk or egg at age 1 year and wheeze at 12 years of age was found. These two studies were enriched with atopy high-risk children, and thus did not represent the general population. In our study, transient sensitization was defined as having elevated s-IgE to the allergen of interest maximum twice, but not at consecutive visits, at 3, 6, 12 or 18 months. Therefore, an association with atopic airway diseases at 14 years could be explained by transient sensitization being present twice rather than once. However, all children with transient sensitization to egg and other allergens were sensitized only once. Another explanation could be that being sensitized at 18 months only, i.e. transient, could be an indicator of later persistent rather than early transient sensitization. Meanwhile, both transient and persistent sensitization to food was present at all visits from 3 to 18 months as shown in Figure 2b. Another possible explanation of the associations could be that these participants had higher levels of s-IgE to egg. Other studies found that s-IgE levels played an important role as a predictor of later development of atopic airway diseases (1, 19, 20). An association between persistent early-life sensitization to cow's milk and asthma at 14 years was seen in this study (aOR=8.90). However, most of the participants with persistent milk sensitization had also persistent sensitization to egg allergens (7/8) and therefore this result must be interpreted with caution. Although, the high odds ratio found indicate that being persistent sensitized to both egg and milk seem to increase the risk of later asthma.

Beside the association between sensitization to egg and atopic airway diseases at 14 years we found an association between transient sensitization to HDM and the development of asthma at 14 years (aOR=3.80). The same conclusion was derived from the MACS study between mono- and poly-sensitization to HDM at age 1 year and wheeze at 12 years (18). The role of sensitization to HDM and the development of asthma has been debated, however, HDM sensitization still has one of the strongest and most consistent associations with asthma in different types of studies from different populations over different time periods and ages (3, 18, 21, 22). In our study there were few cases with coexistence of sensitization to both HDM and milk/egg which therefore could explain the association found in this study

We conducted 4 categories of sensitization to ensure a reference category of not sensitized children. In the group categorized as "other sensitization" the majority were sensitized to wheat allergens, which was not associated to subsequent development of allergic airway diseases later in childhood. This might indicate that the high prevalence of early-life wheat sensitization is a transient phenomenon or that the assay used to analyze s-IgE to wheat was not sufficient specific/too sensitive, which is also indicated in a previous publication with a high degree of clinically irrelevant monosensitization to wheat (23). An association to RC at 14 years was seen in some groups classified as having other sensitization and this might be explained by the influence of those with sensitization to egg allergens.

In our adjusted analysis we included confounders e.g. parental atopy, early atopic dermatitis, food allergy and wheeze and still early sensitization to egg was associated with later development of atopic airway diseases in this unselected population. This indicate that stratifying allergen-specific IgE levels in serum to common food allergens before two years of age can identify children at high risk of developing asthma and RC later in life.

Our study has some limitations. First, our study population was relatively small and since the study population included only 51.3% of those fulfilling the inclusion criteria, there is a risk for selection bias. However, this group did not differ from those that declined participation originally (11). In this study we used a subgroup of the original cohort as our study population and we found that they belonged to a higher social class and were less exposed to maternal smoking during pregnancy and birth time, which may influence the prevalence of atopic diseases. Our study population were all born at the same hospital, as were most infants in that region, and in Denmark at that time 99% were born at a hospital. All were full born with a birthweight > 3000 g, raised in the same area with a homogeneous outdoor environment and the majority (>90%) attended daycare. Thus confounding by a possible environmental biodiversity of the environment was regarded minimal. We found a high prevalence of asthma and RC at 6 and 14 years which may indicate that the sample was enriched with atopic individuals. However, there was no significant differences in the

prevalence of atopic diseases at 3 years between the study population and those excluded, as well as the prevalence found in this study population did not differ significantly from the prevalence reported from the follow-up investigations at 6 and 14 years (10, 12). Therefore, we find that our study population represents the general population. Another limitation is the relative small numbers of participants sensitized from 3 to 18 months, and due to loss of follow-up the number decreased when investigating asthma and RC at 6 and 14 years. Nevertheless, also other studies demonstrated that sensitization to specific allergens in this age group is relatively rare (5, 18, 24). In this study a change of the assay for the measurement of S-IgE was done at 6 years. However, it has been shown that the two methods, Magic Lite and ImmunoCAP, correlate to a high degree (25). Meanwhile, for some food allergens it is well known, that there are variations due to different assays (26), especially regarding wheat (23). The strengths of this study are the frequent follow-up investigations with measurements of s-IgE in the first two years, giving a unique insight in the role of early-life s-IgE. Besides, all diagnoses in the study were predefined and doctor-diagnosed based on clinical examinations, and asthma was not only classified as wheeze but was also objectivized with spirometry when possible.

Conclusion: The ability to produce s-IgE to egg allergens before two years of age both in a transient and persistent way was associated with asthma and rhinoconjunctivitis later in childhood. Furthermore early-life sensitization to HDM was associated with asthma at 14 years. These results show the importance of early-life sensitization to specific allergens as a focus for possible preventive measures.

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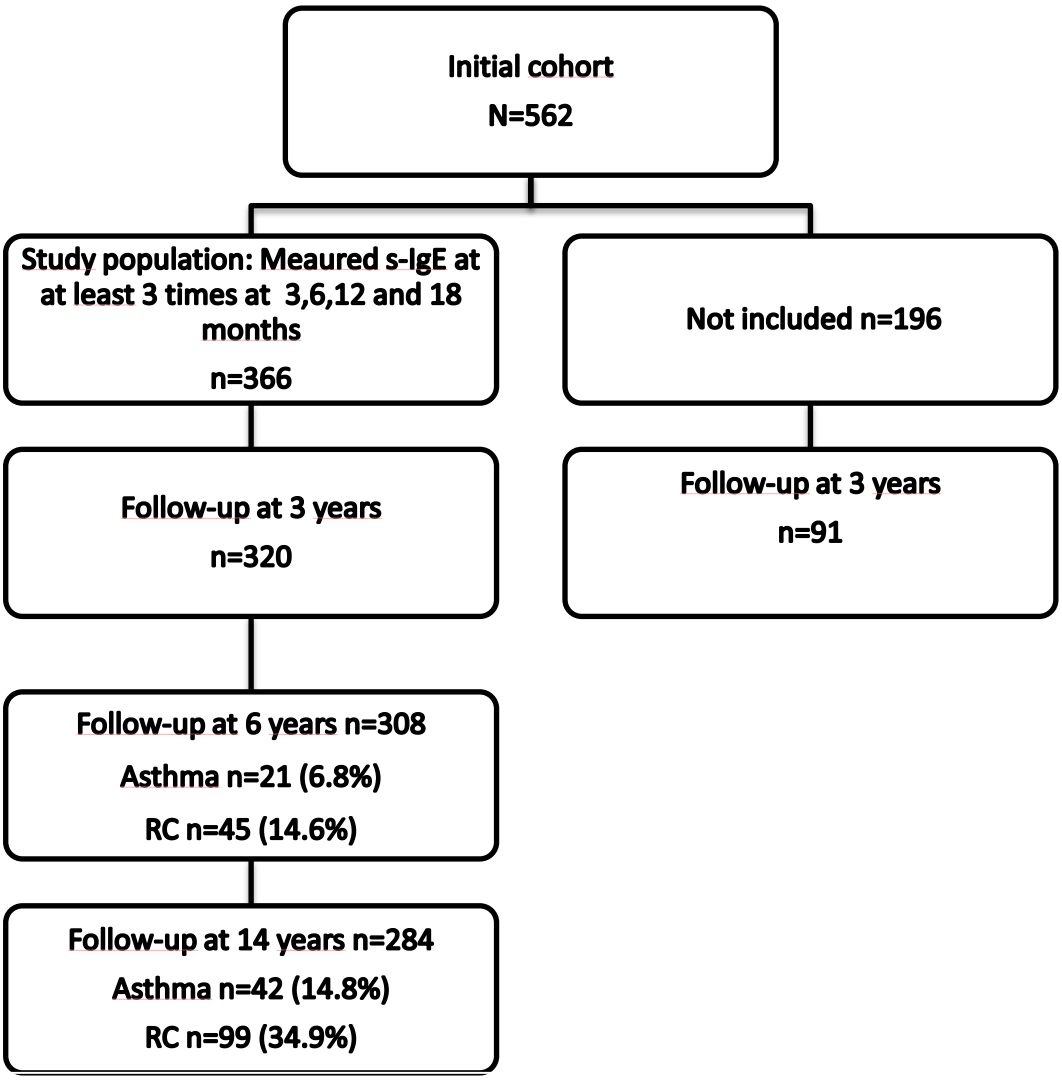
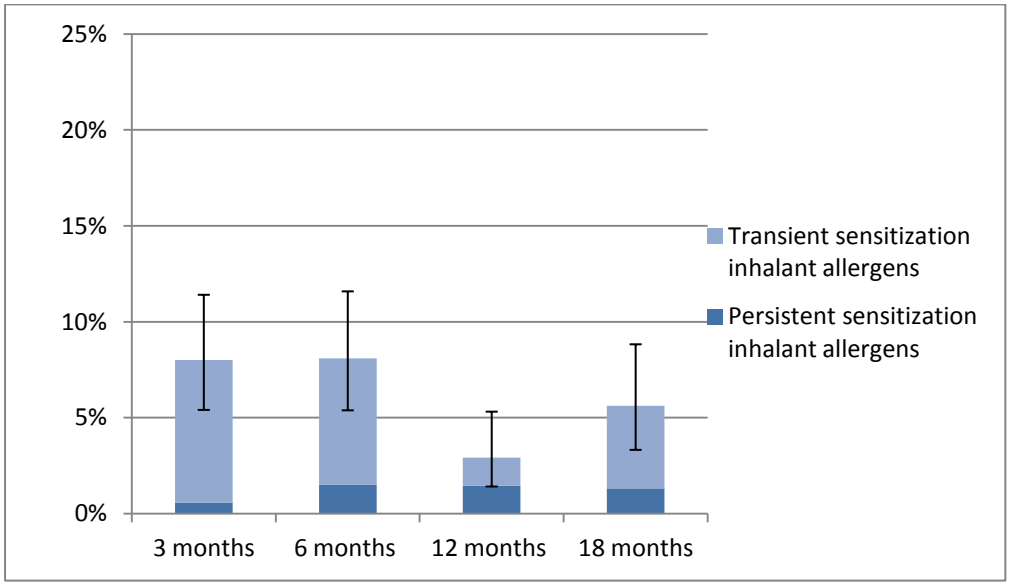
Figure 1: Flowchart of the study



RC: Rhinoconjunctivitis

Figure 2a and 2b: Prevalence of transient and persistent sensitization to inhalant (a) and food (b) allergens at 3, 6, 12 and 18 months of age

2a



2b