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ORIGINAL ARTICLE

Basic and Translational Allergy Immunology

Extract and molecular-based early infant sensitization and associated factors—A PreventADALL study

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Abstract

Background: More knowledge about sensitization patterns in early infancy, including impact of molecular allergology, is needed to help predict future allergy development more accurately.

Objective: We aimed to determine the prevalence and patterns of allergic sensitization at 3 months of age, and explore possible associated factors.

Methods: From the Scandinavian antenatally recruited PreventADALL mother–child cohort, we included 1110 3-month infants with available serum. Sensitization was defined as s-IgE of ≥0.1 kU_A/L by Phadiatop Infant® (ThermoFisher Scientific) including birch, cat, grass, dog, milk, egg, peanut and wheat. Further ImmunoCAP analyses to ovomucoid, casein, Ara h 1-3, omega-5-gliadin were performed in food extract

Abbreviations: 95% CI, 95% confidence interval; Ara h, Arachis hypogea; IgE, immunoglobulin E antibodies; kU_A/L, kilounits of allergen-specific IgE per litre; s-IgE, specific immunoglobulin E antibodies.

Björn Nordlund and Anna Asarnoj shared last authorship.

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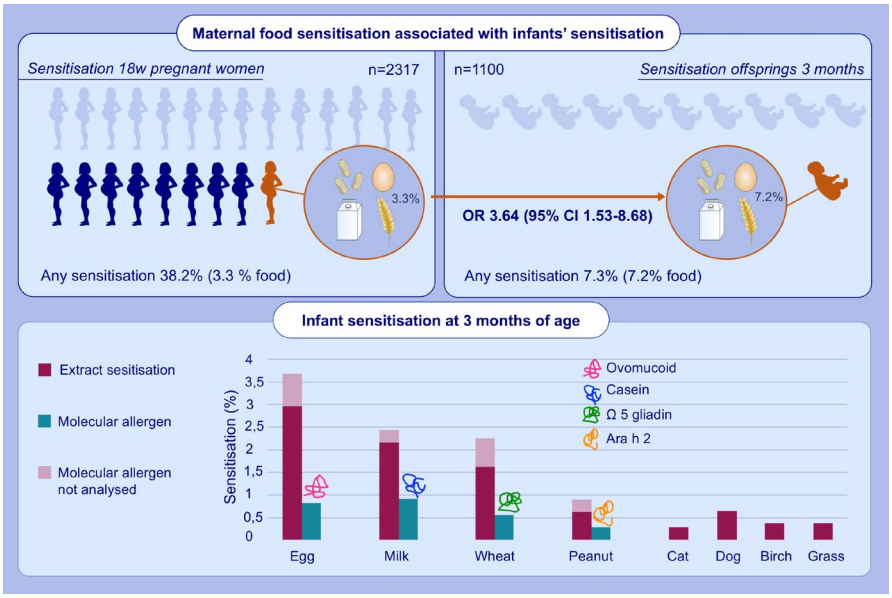
s-IgE-positive children. Maternal sensitization was defined as s-IgE ≥ 0.35 kU_A/L to Phadiatop® (inhalant allergen mix) and/or Fx5 (food allergen mix) at 18-week pregnancy.

Results: Overall 79 (7.3%) infants had specific sensitization, many with low s-IgE-levels (IQR 0.16–0.81 kU_A/L), with 78 being sensitized to food extract allergens; 41 to egg, 27 to milk, 10 to peanut, and 25 to wheat. A total of 62/78 were further analysed, 18 (29%) had s-IgE to ovomucoid, casein, Ara h 1-3 and/or omega-5-gliadin. Eight infants (0.7%) were sensitized to inhalant allergens. Maternal sensitization to food allergens was associated with infant sensitization, odds ratio 3.64 (95% CI 1.53–8.68).

Conclusion: Already at 3 months of age, 7% were sensitized to food, mostly without detectable s-IgE to food allergen molecules, and <1% to inhalant allergens. Maternal food sensitization was associated with infants' sensitization.

KEYWORDS
birth cohort, IgE, immunoglobulin E antibodies, molecular allergology, sensitization



GRAPHICAL ABSTRACT

At 3 months of age, 7% of the infants are sensitized to food, and few of them have detectable s-IgE to food allergen molecules. Very few infants, <1%, are sensitized to inhalant allergens. Maternal food sensitization is associated with infants' sensitization, odds ratio 3.64 (95% CI 1.53–8.68).

Abbreviations: OR, odds ratio; 95 % CI, 95% confidence interval

1 | INTRODUCTION

The development of allergic sensitization, that is presence of allergen-specific immunoglobulin E antibodies (s-IgE), is the basis of many hypersensitivity reactions to food and inhalant allergens and is often a precursor to later development of atopic dermatitis, food allergy, asthma, and allergic rhinitis.[1] The development is dynamic throughout childhood, and the IgE profile seems to affect the course, symptoms and the severity of allergic diseases.[2] However, some individuals develop sensitization without clinical symptoms of allergy.[3] Allergic sensitization can be diagnosed by measuring s-IgE in serum or by skin prick test using allergen extracts. Established in recent years, methods of molecular allergology enable differentiation between cross-reactive or species-specific allergen protein molecules, and allergen protein molecules associated with mild or severe allergic reactions.[4,5]

With the analyses of the allergen protein molecules casein for cow's milk protein,[6] ovomucoid for egg,[7] Ara h 1, Ara h 2, Ara h 3 for peanut,[8] and omega-5-gliadin for wheat,[9] it is now possible to give a more clinically appropriate diagnosis of specific food allergy, when oral food challenge is not feasible.

The exact time point when the child's IgE antibody production starts to develop and can be measured is not clear. Although IgE in cord blood has been found to be identical with maternal IgE, the relationship with the child's own IgE production quickly disappears.[10-12] During the first year of life sensitization develops rapidly. Previous studies have reported that the prevalence rates for any sensitization at 3 months of age vary between 5% and 13%,[13-16] and at 12–18 months, the prevalence of sensitization to at least one allergen ranges between 16% and 21%.[17,18] To our knowledge, documentation of allergic sensitization data in 3-month-old infants in relation to that of their mothers during pregnancy is sparse. Especially, there is a knowledge gap concerning the development of IgE against specific allergen molecules in young children.

The most commonly reported risk factors for the development of sensitization in children older than 1 year include parental atopic history, male gender and atopic dermatitis.[13,19-23] However, it is not clear to what extent allergic sensitization or other atopic traits in the mother impact the development of sensitization in her infant. Furthermore, due to the lack of studies assessing IgE in a large population of young infants, there is a need to identify risk for sensitization and the impact of perinatal and infant factors, including mode of delivery, birth weight, gender and maternal factors such as BMI, smoking, and socio-economic factors.

Birth cohorts are ideal to study the development of atopic disease in children, and antenatal recruitment including data of maternal sensitization and other potential risk factors enables identification of the most prominent risk factors at the start of life.

2 | AIM

Our aim was to determine patterns of allergic sensitization at 3 months of age, and explore whether maternal and perinatal associated risk factors are associated with sensitization in early infancy.

3 | METHODS

3.1 | Study design, setting and population

PreventADALL (Preventing Atopic Dermatitis and ALLergies in Children) is a Nordic population-based mother–child birth cohort where the infants at birth were included in a randomized clinical trial of two interventions (food and skin). Briefly, 2697 pregnant women were recruited at the 18-week routine ultrasound examination from December 2014 until October 2016, in Norway (Oslo and Østfold) and Sweden (Stockholm) as described elsewhere.[24] Inclusion criteria for enrolment in pregnancy were sufficient maternal language skills, singleton or twin pregnancy without severe malformations or disease. Enrolment at gestational week 18 included a brief structured interview, and measurements of height, weight and blood pressure measures as well as blood sampling. The included women completed detailed electronic questionnaires both at enrolment and at 34 weeks of pregnancy including information on socio-demographics, atopic heredity, living conditions, smoking and maternal antenatal health.

Their offspring (N = 2396) were included at birth and randomized to four different groups (skin intervention from 2 weeks of age, early food introduction from 3 months of age, both skin intervention and early food introduction, or controls), given a gestational age of ≥35 and no severe disease. Birth data were collected from birth charts at inclusion of the newborn as described elsewhere.[24] The visit at 3 months of age included anthropometric measurements, clinical examination as well as blood sampling for IgE measures from the participating 1110 infants.

The present study included all 1110 infants who at 3 months of age had available serum for IgE analyses (Figure 1) and their mothers.

3.2 | Sensitization measurements

Blood samples from the pregnant women were collected at inclusion around 18 weeks gestational age, set for one hour, spun for serum extraction, aliquoted and stored at −80°C until analysed for allergen-specific IgE levels using ImmunoCAP (Thermo Fischer Scientific): from the Phadiatop® (birch, cat, dog, horse, grass, mugwort, house dust mites (*Dermatophagoides pteronyssinus*), and *Cladosporium herbarum*) and Fx5 (cow's milk, egg white, wheat, peanut, cod). If a sample scored positive IgE ≥ 0.35 kU_A/L to one of the mixes, further analyses of specific IgE towards allergens included in the mixes were performed. Allergic sensitization in women was defined as IgE levels ≥0.35 kU_A/L. In this study, results from specific IgE against cod, horse or *Cladosporium herbarum* were not used.

Blood samples were collected from the infants at the 3 months visit, set for one hour, spun for serum extraction, aliquoted and stored at −80°C until analysis of specific (s-) IgE to food and inhalant allergens first by using ImmunoCAP Phadiatop Infant® (birch, cat, dog, grass, cow's milk, egg white, peanut). In case of positive Phadiatop Infant (≥0.1 kU_A/L), s-IgE to each allergen in the mix was further analysed. Additionally, s-IgE to wheat extract was analysed in all infants with available sera. In infants that scored positive to whole extract (IgE ≥ 0.1 kU_A/L), we further analysed relevant allergen components within the food allergens; for egg ovomucoid (Gal d 1), for milk casein, for peanut Ara h 1, Ara h 2 and Ara h 3, and for wheat omega-5-gliadin. Infant sensitization was defined as an allergen-specific IgE level of ≥0.1 kU_A/L.

3.3 | Definition of maternal and perinatal exposures

Maternal history of atopic dermatitis, allergic rhinitis, asthma and food allergy at the time of study inclusion (18 weeks) was defined as self-reported doctor confirmed diagnosis of each relevant disease.

Previous deliveries were defined as at least one previous delivery at inclusion.

Low maternal age was defined as age below 25 years at inclusion.

Maternal BMI was defined as mother's weight in kilograms divided by mother's length in squared metres (kg/m^2), measured at time of inclusion.

Maternal smoking was defined as answer 'yes' to the questions 'have you ever smoked' and 'do you smoke currently' specified as 'smoked during pregnancy', 'smoked but quit recently' or 'smoked but quit whilst trying to get pregnant' at time of study inclusion.

Furry pet at home was defined by the answer 'yes' to the question concerning having a pet at study inclusion time.

Low maternal education level was defined as preliminary school only (9/10 years) or less education years.

Low family income was defined as below 300,000 Norwegian/Swedish crowns (kroner/kronor)/year.

Study country was defined as participant enrolled in Sweden or Norway, respectively.

Delivery mode was defined as caesarean section or vaginal delivery.

Low birthweight was defined as a birth weight below 2500 g.

Low gestational age at birth was defined as birth between 35 and 37 weeks of gestational age.

3.4 | Statistical analyses

Prevalence rates are expressed as numbers and proportions (as a percentage). The chi-squared test was used for comparison of dichotomous variables between groups. The Fisher exact test was used if one comparison group consisted of 5 observations or less. Group IgE levels were expressed as median values and interquartile ranges. Two-tailed *t* test was used on log transformed values for group comparisons of IgE levels. $p < 0.05$ were considered significant. Odds ratios (OR) with 95% confidence intervals (CIs) were calculated using logistic regression for the association of sensitization in relation to background factors. In the first step, univariate (crude) analyses were made for each available maternal or perinatal factor known from the literature or clinical knowledge to be of potential importance for allergy development. All estimates with a *p*-value of 0.2 or below were then in a second multivariate analysis included in the adjusted model (*infant gender, pet at home, low birth weight, maternal sensitization, maternal food sensitization*). Statistical analyses were conducted using STATA Statistical Software (16.0).

3.5 | Ethics

Ethical approval for the PreventADALL study was obtained by the regional ethics committee in Stockholm, Sweden, (nr: 2014/2242-31/4) and the Regional Committee for Medical and Health Research Ethics in South-Eastern Norway (2014/518), and signed informed consent were collected from the women and from both parents

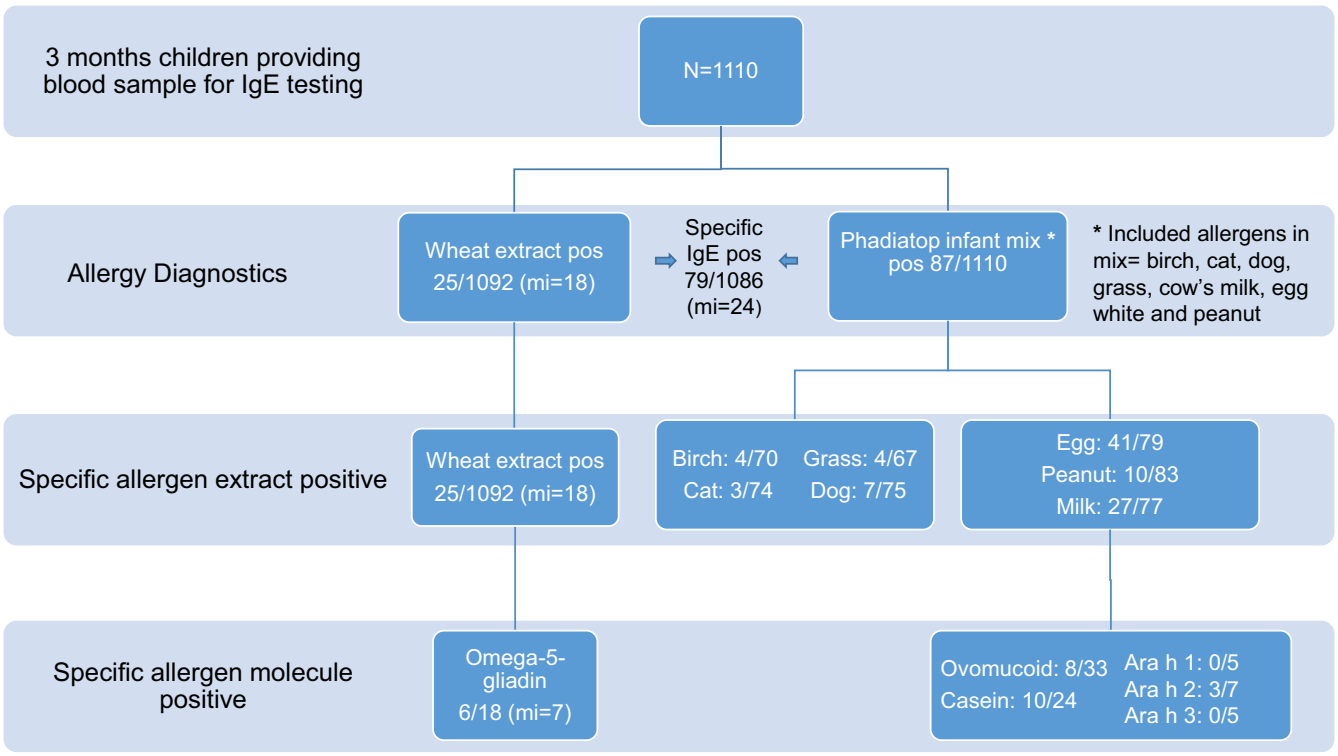


FIGURE 1 Flow chart of the selection of the study cohort with details of available child blood samples and subsequent analysis of specific allergen extract and specific allergen molecules, with cut-off ≥0.1 kU_A/L)

of the infants. PreventADALL is registered in ClinicalTrials.gov, Identifier: NCT02449850.

4 | RESULTS

A flow chart of the entire cohort is presented in online repository Figure S2. In general, the participating expectant mothers were well educated, lived with a partner and were mainly of urban population, as previously reported by Carlsen et al.[24] The background characteristics for the 1100 infants with available serum were not significantly different from those who did not have available serum (*n* = 1286) and who were therefore not included in the present study (Table 1).

Analysis of Phadiatop infant was available for all 1110 infants, s-IgE to wheat in 1092 and s-IgE to the specific allergens within the Phadiatop Infant in 1086 infants as shown in Figure 1. Overall, 87/1110 infants had a positive Phadiatop infant mix (including birch, cat, dog, grass, cow's milk, egg white and peanut allergens), while 25 of the 1092 had s-IgE to wheat IgE.

As presented in Table S1, 7.3% (*n* = 79) of 1086 infants with sufficient amount of sera for allergen-specific IgE-analysis were sensitized to at least one specific allergen, with median s-IgE levels among all positive s-IgE values of 0.23 kU_A/L (IQR 0.16–0.81 kU_A/L). All, but one of these infants (78/79) were sensitized to a food allergen, most commonly to egg (3.7%), but also to cow's milk (2.5%), wheat (2.3%) and peanut (0.9%), Figure 2.

Among the 78 food-sensitized infants, 62 children's sera were available for further analysis: only 18/62 (29%) were identified with s-IgE to a food allergen molecule. In the 41 infants with s-IgE to egg, 8/33 (24%) with sufficient serum for further analyses were sensitized to ovomucoid, Figure 2. In infants with s-IgE towards milk 10/24 (42%) were sensitized to casein, and in infants with s-IgE to wheat 6/18 (33%) were sensitized to omega-5-gliadin. Among the infants with s-IgE towards peanut, 3/7 (43%) were sensitized to Ara h2. No infants presented with sensitization towards Ara h1 or Ara h3.

In five of the eight infants who were sensitized to ovomucoid, s-IgE to egg white was 1.0 kU_A/L or above. Similar patterns with higher food extract IgE levels in allergen molecule sensitized infants was seen for milk, wheat and peanut, but with few observations, not permitting statistical analyses.

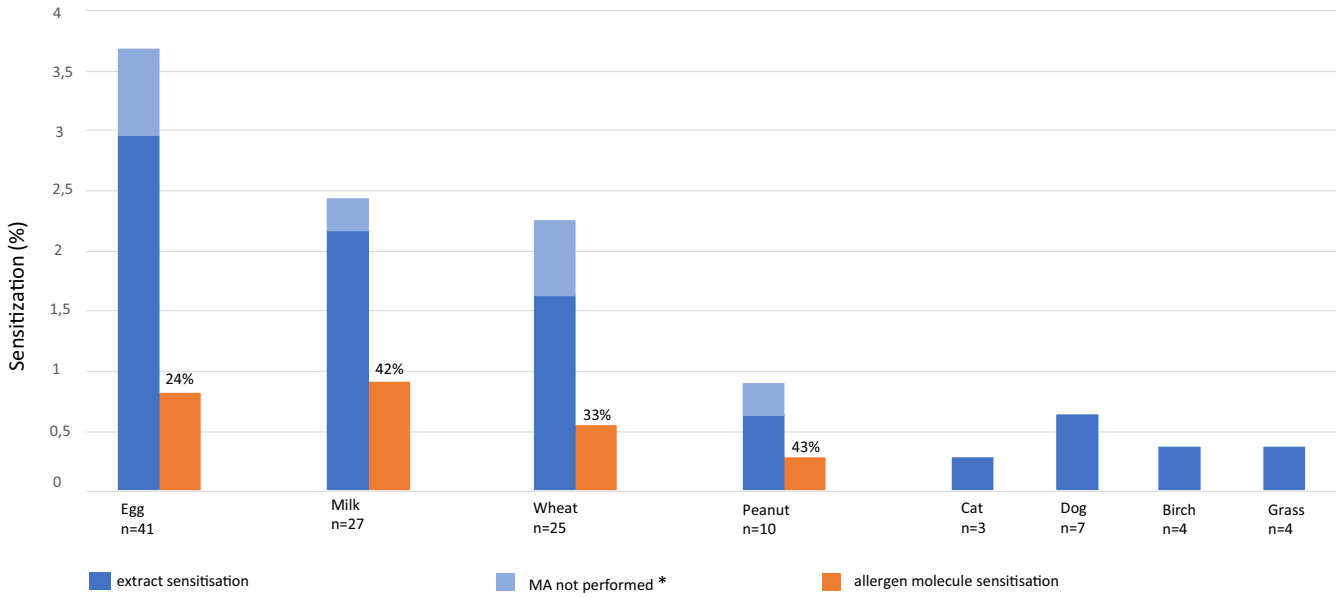
Less than one percent of infants were sensitized to inhalant allergens, most commonly towards dogs, observed in seven infants (0.7%) and to birch in four infants (0.4%). One infant was exclusively sensitized to inhalant allergen, namely to dog. While 59 of the sensitized infants (75%) were sensitized to one allergen only (mono-sensitized), 20 (25%) were polysensitized with 12 infants (14%) sensitized to two and 8 infants (10%) sensitized to three or more allergens, respectively, online repository (Figure S1).

Maternal allergic sensitization as well as other general background characteristics and reported allergic diseases are presented for the mother–child cohort as well as for all women enrolled in the PreventADALL study for comparison in online repository text, Tables S2 and S3 and Figures S2–S6.

The sensitization pattern within mother–child pairs differed significantly, with infants dominantly sensitized to food allergens while the pregnant women were mostly sensitized to inhalant allergens, Figure 3. Infants who were sensitized had more often mothers

TABLE 1 General characteristics of study cohort infants, *N* = 1110 versus no blood sample cohort *N* = 1286 and entire cohort *N* = 2396

	Study cohort (*N* = 1110)		No blood sample (*N* = 1286)		Original cohort (*N* = 2396)	
	n	% (95% CI)	*n*	% (95% CI)	*n*	% (95% CI)
Study country (*N* = 1110/2396)						
Norway	806	72.6 (69.9–75.2)	1073	83.4 (81.3–85.4)	1879	78.4 (76.7–80.0)
Sweden	304	27.4 (24.7–30.1)	213	16.5 (14.6–18.7)	517	21.6 (19.9–21.3)
Male sex (*N* = 1110/2396)	615	55.5 (52.5–58.4)	642	49.9 (47.1–52.7)	1258	52.5 (50.5–54.5)
Delivery mode (*N* = 1110/2396)						
Vaginal delivery	925	83.8 (81.0–85.4)	1074	83.5 (81.4–85.5)	1999	83.4 (81.9–84.9)
Caesarean section	185	16.7 (14.5–19.0)	212	16.5 (14.5–18.6)	397	16.6 (15.1–18.1)
Birth weight (*N* = 1104/2386)						
Low <2500 g	16	1.4 (0.8–2.3)	23	1.8 (1.1–2.7)	39	1.6 (1.2–2.2)
2500–4499 g	1058	95.8 (94.5–96.9)	1223	95.4 (94.1–96.5)	2281	95.6 (94.6–96.4)
>4500 g	30	2.7 (1.8–3.8)	36	2.8 (1.9–3.9)	66	2.8 (2.1–3.5)
Gestational age (*N* = 1092/2347)						
Low <37 weeks	132	12.1 (10.2–14.2)	141	11.6 (10.4–13.0)	273	11.6 (10.4–13.0)
37–41 weeks	938	85.9 (83.7–87.9)	1088	86.7 (84.7–88.5)	2026	86.3 (84.8–87.7)
42 weeks	22	2.0 (1.3–3.0)	26	2.1 (1.3–3.0)	48	2.1 (1.5–2.7)
	Days old (IQR)		Days old (IQR)		Days old (IQR)	
Median age at 3 m visit, days (IQR)	93.0 (IQR 87–97)		92.5 (IQR 88–97)		92.8 (IQR 88–97)	



* MA=molecular allergology not performed, no analysis made for allergen molecules due to lack of sera

FIGURE 2 Specific IgE sensitization (≥0.1 kU_A/L) prevalence in children 3 months of age (%) *N* = 79 and co-existing allergen molecule sensitization, MA, missing allergen, no analysis made for allergen molecules due to lack of sera

with food sensitization (12%) than did non-sensitized infants (3.5%) ($p < 0.001$), while maternal sensitization to inhalant allergens was similar among sensitized (43%) and non-sensitized infants (37%) ($p > 0.2$). Among the sensitized infants, seven had mothers who were sensitized to peanut, of whom four reported a peanut allergy, while none of these infants were sensitized to peanut.

Sensitization at 3 months of age was significantly associated only with maternal food sensitization in logistic regression, remaining significant after adjusting for the other covariates (adj OR 3.64, 95% CI 1.53–8.68) (Table 2). None of the other maternal and perinatal factors were significantly associated with infant sensitization. No correlation was found between the number of sensitizing allergens in the mothers and sensitization in the infants. As the skin intervention was implemented from 2 weeks of age, we stratified allergic sensitization by skin intervention, observing similar sensitization among infants in the skin intervention group (6.7%) and the non-skin intervention group (7.7%) ($p = 0.557$).

5 | DISCUSSION

5.1 | Main findings

This is to our knowledge the first time a large international population-based mother–child cohort has provided specific IgE as well as allergen molecule data from young infants. Seven per cent of infants at 3 months of age had sensitization towards foods, most commonly to egg, while sensitization to inhalant allergens was observed in less than one percent. In contrast, their mothers had mostly IgE towards inhalant allergens during mid-pregnancy. Further, few infants expressed IgE to food allergen molecules at this age. Maternal food sensitization was found to be a significant risk factor for infant sensitization.

Our finding that infants express s-IgE already at 3 months of age, although at low levels, is in line with earlier studies,[14,21] Previous studies, such as the BEAT study,[25] measured sensitization by skin prick test, not enabling direct comparison of levels between the studies. The infants in our study were mostly sensitized to food allergens, with <1% being sensitized to inhalant allergens. The prevalence of any sensitization in our study was lower than earlier described by the Danish population-based DARC study of 562 children[13] who reported 12.5% prevalence of any sensitization, but slightly higher than the nine centre Norwegian Bronchiolitis study who studied 368 bronchiolitis patients and 224 healthy controls and found that 5.5% had allergen-specific IgE antibodies at age 0–3 months.[16]

Our rates of s-IgE towards milk (2.5%) and egg (3.7%) where higher than in the DARC study that found s-IgE towards milk in 1.7% and towards egg in 2.5% of the infants at 3 months of age,[13] and more in line with the Australian BEAT study who followed 319 infants at risk for allergy, where 3.9% were sensitized to egg measured by skin prick test at 4 months of age.[25]

The prevalence of a reported doctor diagnosis of asthma, atopic dermatitis and food allergy among pregnant women was higher in our cohort compared to other population-based studies, possibly due to a slight bias towards allergic women being more likely to participate in a study aiming at primary prevention of allergic diseases. Additionally, differences between countries or slightly different definitions for the specific diagnoses could also explain variation

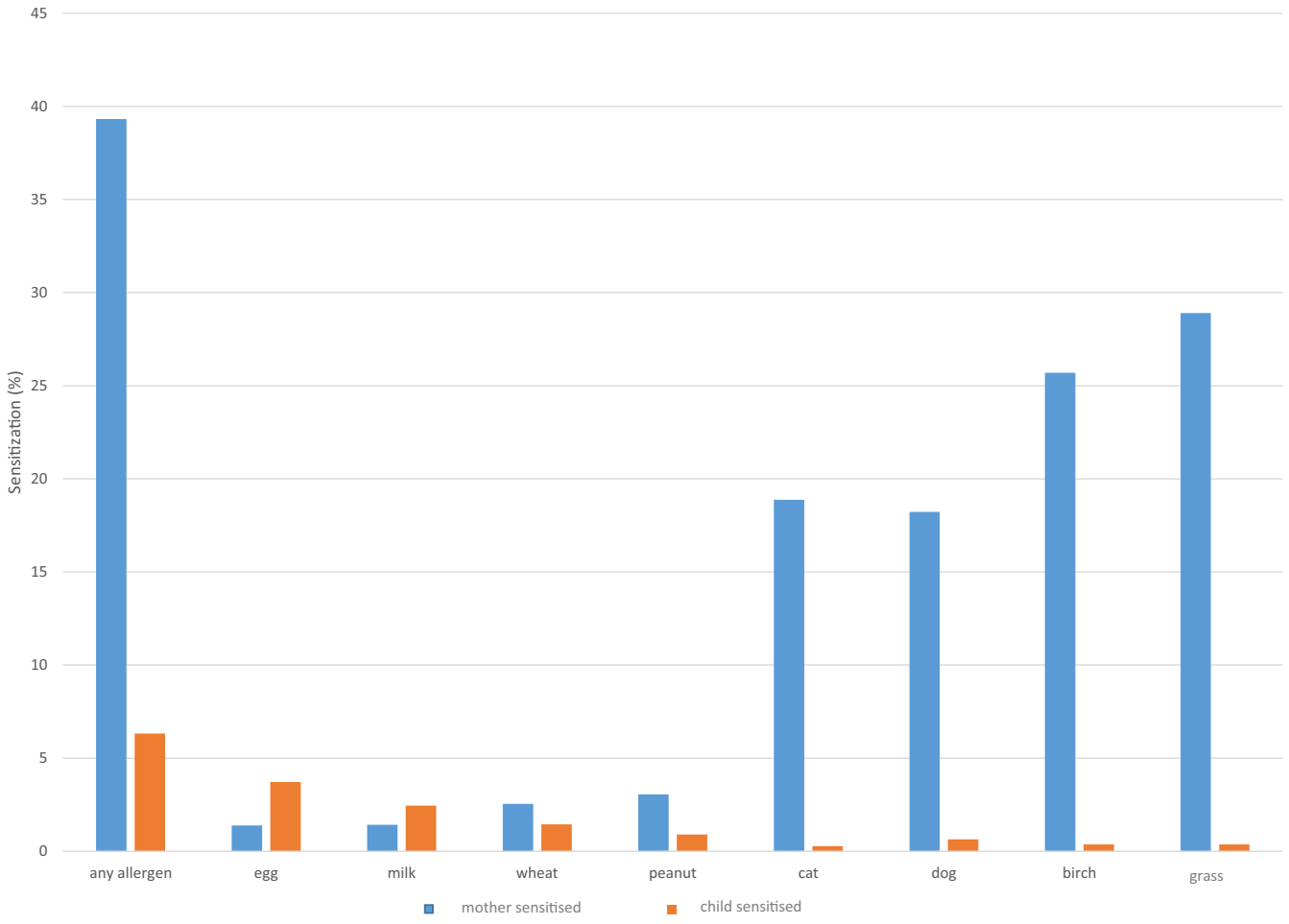


FIGURE 3 Specific IgE sensitization prevalence among pregnant women (≥0.35 kU_A/L) and children (≥0.1 kU_A/L) at 3 months of age, *N* = 1100, (%)

between studies, even though most comparable studies used similar self-reported questionnaires.[26,27] However, for allergic rhinitis the reported prevalence was lower in our study (20%) as compared to the Japanese JECS study that reported 36% of 99,103 pregnant women to suffer from allergic rhinitis.[27] The women mainly presented IgE towards inhalant allergens, and the prevalence in the present study of any sensitization of 37.2% was almost identical to what Melén et al[28] found in 24-year-old women in the Swedish birth cohort BAMSE (*n* = 1244), possibly due to the fact that both cohorts included Scandinavian populations only. This correlates quite well to the 35% sensitization prevalence by SPT found by in an adult swedish cohort.[29] We found s-IgE towards peanut to be the most common food allergen (in 2.6%), in contrast the s-IgE rate towards egg was only 0.6%, which is lower than a previous study that presented data on s-IgE towards food allergen, reporting a sensitization prevalence towards egg in 1%.[27]

We identified maternal food sensitization as a risk factor for early infant sensitization, with a three-fold increased risk. Similar findings were reported in the PASTURE birth cohort, were infants from five different European countries were followed between birth and 12 months of age.[23] Other risk factors for early sensitization reported by others, such as male gender,[14] could not be confirmed in our study.

Several previous studies have investigated the correlation between maternal IgE during pregnancy, cord blood IgE and early sensitization in the infant, with conflicting results regarding an association with maternal sensitization.[10-12,30-32] In the present study, we have not used cord blood IgE. Previous findings mainly found IgE cord blood profiles originating from the mother, indicating no own production of allergen s-IgE from the child at birth. Bonnelykke et al reported no relation between maternal IgE profile and infant IgE at 6 months.[33] After evaluating our IgE data from the mothers and the infants at 3 months with clearly different IgE patterns, the s-IgE detected at 3 months of age represents infants' own IgE production.

5.2 | Strengths and limitations

Among the strengths of the present study is the population-based design and the relatively large size of the study population. Additionally, it is a multi-centre study and comprises a vast number of prospectively collected data, including extensive antenatally

TABLE 2 Maternal and perinatal factors associated with any infant sensitization at 3 months of age (inhalant or food specific IgE ≥ 0.1 kU_A/L) *N* = 79

	n/N (%)	Crude OR (95% CI)	Adjusted[a] OR (95% CI)
Offspring gender (ref female)	492/1104 (44.6)	0.60 (0.41–1.07)	0.68 (0.40–1.13)
Maternal sensitization (any, ≥0.35 kU_A/L)	399/1065 (37.4)	1.42 (0.88–2.28)	1.13 (0.66–1.94)
Maternal food sensitization (any, ≥0.35 kU_A/L)	44/1068 (4.1)	3.67 (1.69–7.96)	3.64 (1.53–8.68)
Maternal inhalant sensitization (any, ≥0.35 kU_A/L)	404/1068 (37.8)	1.28 (0.80–2.06)	
Study country (ref Norway)	802/1104 (72.6)	1.04 (0.62–1.75)	
Low education	101/999 (10.1)	1.12 (0.52–2.41)	
Low income	7/1104 (0.6)	0.66 (0.31–1.40)	
Maternal tobacco use	274/1005 (27.3)	1.43 (0.85–2.43)	
Maternal BMI >25	423/1090 (38.8)	0.89 (0.55–1.44)	
Maternal BMI >30	95/1090 (8.7)	0.88 (0.37–2.07)	
Pets at home	230/1005 (22.9)	0.30 (0.35–1.11)	0.50 (0.24–1.03)
Maternal allergy (any)	632/1005 (62.9)	1.35 (0.84–2.17)	
Maternal asthma, rDD	164/1005 (16.3)	1.24 (0.67–2.27)	
Maternal food allergy, rDD	128/1005 (12.7)	1.38 (0.72–2.64)	
Maternal atopic dermatitis, rDD	183/1005 (18.2)	1.40 (0.79–2.47)	
Maternal allergic rhinitis, rDD	212/1005 (21.1)	0.88 (0.48–1.61)	
Caesarean section (ref PN)	185/1104 (16.7)	1.28 (0.72–2.28)	
Previous deliveries (ref 0)	410/555 (73.9)	1.25 (0.58–2.68)	
Low gestational age (<37 weeks)	131/1086 (12.1)	0.69 (0.31–1.54)	
Low birth weight (<2500 g)	16/1098 (1.4)	3.05 (0.85–10.95)	3.59 (0.70–18.38)

Abbreviations: PN, vaginal delivery; rDD, self-reported doctor diagnose.

[a]Adjusted for variables with association *p*-values of 0.2 or less in the univariate analyses: infant gender, pet at home, low birth weight, maternal sensitization, maternal food sensitization.

recorded baseline data regarding maternal atopic history. It also encompasses sensitization data from both mothers and infants, and especially on the molecular allergen level that is unique in such small infants.

One of the limitations is the cut-off level ≥0.35 kU_A/L of the Phadiatop and Fx5 allergen mixes used for analysing sensitization in the pregnant women. The samples were not analysed for individual allergens if the mixes did not pass this level. However, the cut-off ≥0.35 is in the one currently used in clinical setting for Phadiatop. Since most previous research has used a cut-off ≥0.35 kU_A/L, it also allows us to compare our results with other studies.

Blood sampling at 3 months of age in a general infant cohort is challenging, with an insufficient amount of serum in 16.4% rendering some IgE analyses incomplete. As a consequence, we cannot rule out a slight underreporting of allergic sensitization in our study, although we did prioritize food allergens for analyses. IgE for wheat was analysed separately in the infants since wheat extract was not included in the original Phadiatop Infant mix. Thus, all included infants were analysed for wheat, not only those positive in the Infant mix, which was the procedure for all other analysed allergens. This might have resulted in the numbers of positive IgE to wheat cases to be slightly overrepresented.

In addition to being an observational study, The PreventADALL study is a randomized clinical trial with the skin intervention starting at 2 weeks of age, thus preceding blood sampling at 3 months of age. We therefore stratified analyses by skin intervention, but found no significant differences among infants in the skin intervention group and the non-interventional group. While some individuals theoretically could have started food introduction before age 3 months, outside the study protocol, we have no reason to assume this would be different depending on intervention group.

Our results of maternal sensitization of 38.2% correlates well to other similar cohorts,[28-29] and this together with the large study sample and settings of the PreventADALL indiqates that the generalizability is adequate and the results reproducible in other cohorts with similar settings.

5.3 | Clinical implication and future research

At 3 months of age, less than 30% of food extract sensitized infants express s-IgE antibodies to clinically relevant allergen molecules with a possible implication of tolerance development to these foods. Our finding of an association between infant sensitization and maternal

food sensitization might indicate that an early intervention could be even more beneficial in infants born to mothers with food allergy. Further studies are needed, especially regarding the influence of early food introduction and the length of the 'window of opportunity'. Early introduction of allergenic foods has been associated with a lower risk of developing food allergy in subsets of infants at high risk[34] or in observational studies,[35] while a randomized trial in a general population-based study failed to replicate the reduced risk of food allergy.[15] Consequently, some advice against delaying complementary food introduction, in order to initiate oral tolerance.[36,37] The general population-based PreventADALL study will be further explored for the possible impact of early complementary food introduction to reduce food allergy in sensitized and non-sensitized infants.

6 | CONCLUSION

At 3 months of age, seven per cent of infants from a general population were sensitized to food allergens and less than one percent to inhalant allergens, while s-IgE to food allergen molecules was observed in around one of three infants sensitized to food allergens. In contrast, sensitization to inhalant allergens was most common among their mothers in mid-pregnancy. Maternal food sensitization was found to be a significant risk factor for 3 months sensitization among the infants.

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CONFLICT OF INTEREST

M.P Borres is an employee of Thermo Fisher Scientific. M van Hage has received lecture fees from Thermo Fisher Scientific outside the submitted work. None of the other authors have any conflict of interest to declare.

AUTHOR CONTRIBUTIONS

Sandra Tedner and Anna Asarnoj participated in design of the study, data analysis, and manuscript writing and contributed to data collection. Karen Eline Stensby Bains, Martin Färdig, Sabina Wärnberg Gerdin, Hrefna Katrín Gudmundsdóttir, Ina Kreyberg, Live Solveig Nordhagen and Eva Maria Rehbinder contributed to data collection, critically reviewed data and revised the manuscript. Magnus P. Borres and Karin C. Lødrup Carlsen participated in design of the study, critically reviewed data and revised the manuscript. Kai-Håkon Carlsen participated in developing and running of the PreventADALL study, critically reviewed data and revised the manuscript. Guttorm Haugen contributed to running the study, critically reviewed data analysis and revised the manuscript. Karin CL Carlsen and Gunilla Hedlin participated in initiating, developing the concept, design and establishment of the study, critically reviewed data and revised the manuscript. Jon Konradsen contributed to the conception, planning, critically reviewed data and revised the manuscript. Christine Monceyron Jonassen participated in developing the concept, design and establishment of the PreventADALL study, critically reviewed data analysis and revised the manuscript. Caroline-Aleksi Olsson Mägi contributed to data collection, management of the study in Stockholm, Sweden, and critically reviewed data and revised the manuscript. Björn Nordlund contributed to the conception, planning and running of the study, critically reviewed data and revised the manuscript. Knut Rudi and Annetine Staff participated in developing the concept, design and establishment of the PreventADALL study, critically reviewed data and revised the manuscript. Håvard O. Skjerven contributed to the conception, planning and running of the study, critically reviewed data and revised the manuscript. Cilla Söderhäll participated in developing the concept, design genetic and epigenetic sampling and analysis procedures in the study, critically reviewed data and revised the manuscript. Marianne van Hage contributed to the conception, planning of the analyses, critically reviewed data and revised the manuscript. Riyas Vettukattil contributed to managing the database, critically reviewed data and revised the manuscript. Björn Nordlund participated in initiating, developing the concept, design, establishment and running of the study, critically reviewed data and revised the manuscript. All authors have approved the last version before submission.

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SUPPORTING INFORMATION

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

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