

Extract and molecular-based early infant sensitisation and associated factors – a PreventADALL study

Short title: *Extract and molecular-based early infant sensitisation*

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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.

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Abstract:

Background

More knowledge about sensitisation 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 sensitisation at three months of age, and explore possible associated factors.

Methods

From the Scandinavian antenatally recruited PreventADALL mother-child cohort we included 1110 three-months-infants with available serum. Sensitisation was defined as s-IgE of ≥ 0.1 kU_A/l by Phadiatop Infant® (ThermoFisher Scientific, Sweden) 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 s-IgE-positive children. Maternal sensitisation 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 sensitisation, many with low s-IgE-levels (IQR 0.16-0.81 kU_A/l), with 78 being sensitised to food extract allergens; 41 to egg, 27 to milk, 10 to peanut, and 25 to wheat. 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 sensitised to inhalant allergens. Maternal sensitisation to food allergens was associated with infant sensitisation, odds ratio 3.64 (95% CI 1.53-8.68).

Conclusion

Already at three months of age, 7% were sensitised to food, mostly without detectable s-IgE to food allergen molecules, and <1% to inhalant allergens. Maternal food sensitisation was associated with infants' sensitisation.

Key words:

Immunoglobulin E antibodies, IgE, sensitisation, birth cohort, molecular allergology

Word count: 233

Abbreviations

Ara h: *Arachis hypogea*

IgE: Immunoglobulin E antibodies

kU_A/L: kilounits of allergen-specific IgE per liter

s-IgE: specific Immunoglobulin E antibodies

95% CI: 95% Confidence interval

INTRODUCTION

The development of allergic sensitisation, i.e. 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 sensitisation without clinical symptoms of allergy.³ Allergic sensitisation 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 wheat⁹ it is now possible to give a more clinically appropriate diagnosis of specific food allergy, when oral food challenge is not feasible.

The exact timepoint 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 sensitisation develops rapidly. Previous studies have reported that the prevalence rates for any sensitisation at 3 months of age vary between 5-13%¹³⁻¹⁶ and at 12-18 months the prevalence of sensitisation to at least one allergen range between 16-21%.^{17,18} To our knowledge, documentation of allergic sensitisation data in three-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 sensitisation in children older than one year include parental atopic history, male gender and atopic dermatitis.^{13,19-23} However, it is not clear to what extent allergic sensitisation or other atopic traits in the mother impact the

development of sensitisation 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 sensitisation and the impact of perinatal and infant factors, including mode of delivery, birth weight, gender as well as maternal factors such as BMI, smoking, and socioeconomic factors.

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

AIM

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

METHODS

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 two weeks of age, early food introduction from three months of age, both skin intervention & early food introduction, or controls), given a gestational age of ≥ 35 and no severe disease. Birth data was collected from birth charts at inclusion of the new-born as described elsewhere.²⁴ The visit at three 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 three months of age had available serum for IgE analyses (Figure 1) and their mothers.

Sensitisation 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, Uppsala, Sweden): 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 sensitisation 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 three 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 sensitisation was defined as an allergen-specific IgE level of ≥ 0.1 kU_A/l.

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 meters (kg/m²), 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 grams.

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

Statistical analyses

Prevalence rates are expressed as numbers and proportions (as a percentage). The Chi square 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-values of less than 0.05 were considered significant. Odds ratios (OR) with 95% confidence intervals (CIs) were calculated using logistic regression for the association of sensitisation 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 sensitisation, maternal food sensitisation*). Statistical analyses were conducted using STATA Statistical Software (16.0).

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

RESULTS

A flow chart of the entire cohort is presented in online repository Fig 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 Fig 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 sensitised 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 sensitised 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%), Fig 2.

Among the 78 food sensitised 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 sensitised to ovomucoid, Fig 2. In infants with s-IgE towards milk 10/24 (42%) were sensitised to casein, and in infants with s-IgE to wheat 6/18 (33%) were sensitised to omega-5-gliadin. Among the infants with s-IgE towards peanut 3/7 (43%) were sensitised to Ara h2. No infants presented with sensitisation towards Ara h1 or Ara h3.

In five of the eight infants who were sensitised 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 sensitised infants was seen for milk, wheat and peanut, but with few observations, not permitting statistical analyses.

Less than one percent of infants were sensitised 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 sensitised to inhalant allergen, namely to dog. While 59 of the sensitised infants (75%) were sensitised to one allergen only (mono-sensitised), 20 (25%) were polysensitised with 12 infants (14%) sensitised to two and 8 infants (10%) sensitised to three or more allergens respectively, online repository Fig S1.

Maternal allergic sensitisation 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-S3 and Figures S2-S6.

The sensitisation pattern within mother-child pairs differed significantly, with infants dominantly sensitised to food allergens while the pregnant women were mostly sensitised to inhalant allergens, Fig 3. Infants who were sensitised had more often mothers with food sensitisation (12%) than did non-sensitised infants (3.5%) ($p < 0.001$), while maternal sensitisation to inhalant allergens was similar among sensitised (43%) and non-sensitised infants (37%) ($p > 0.2$). Among the sensitised infants, seven had mothers who were sensitised to peanut, of whom four reported a peanut allergy, while none of these infants were sensitised to peanut.

Sensitisation at three months of age was significantly associated only with maternal food sensitisation 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 sensitisation. No correlation was found between the number of sensitising allergens in the mothers and sensitisation in the infants. As the skin intervention was implemented from two weeks of age, we stratified allergic sensitisation by skin intervention, observing similar sensitisation among infants in the skin intervention group (6.7 %) and the non-skin intervention group (7.7 %) ($p = 0.557$).

DISCUSSION

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 percent of infants at three months of age had sensitisation towards foods, most commonly to egg, while sensitisation 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 sensitisation was found to be a significant risk factor for infant sensitisation.

Our finding that infants express s-IgE already at three months of age, although at low levels, is in line with earlier studies.^{14,21} Previous studies, such as the BEAT study,²⁵ measured sensitisation by skin prick test, not enabling direct comparison of levels between the studies. The infants in our study were mostly sensitised to food allergens, with less than 1% being sensitised to inhalant allergens. The prevalence of any sensitisation in our study was lower than earlier described by the Danish population based DARC study of 562 children¹³ who reported 12.5% prevalence of any sensitisation, 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.²⁶

Our rates of s-IgE towards milk (2.5%) and egg (3.7%) were 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 three 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 sensitised to egg measured by skin prick test at four 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 between

studies, even though most comparable studies used similar self-reported questionnaires.^{27,28}

However, for allergic rhinitis the reported prevalence was lower in our study (20 %) as compared to the Japanese JECS study that reported 36% of 99103 pregnant women to suffer from allergic rhinitis.²⁸ The women mainly presented IgE towards inhalant allergens, and the prevalence in the present study of any sensitisation of 37.2% was almost identical to what Melén et al^{29,30} 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 % sensitisation prevalence by SPT found by in an adult swedish cohort ³¹. 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 sensitisation prevalence towards egg in 1%.²⁸

We identified maternal food sensitisation as a risk factor for early infant sensitisation, with a three-fold increased risk. Similar findings were reported in the PASTURE birth cohort, where infants from five different European countries were followed between birth and 12 months of age.²³ Other risk factors for early sensitisation 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 sensitisation in the infant, with conflicting results regarding an association with maternal sensitisation.^{10-12,32-34} 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 six months.³⁵ After evaluating our IgE data from the mothers and the infants at three months with clearly different IgE patterns, the s-IgE detected at three months of age represents infants' own IgE production.

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 recorded baseline data regarding

maternal atopic history. It also encompasses sensitisation 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 sensitisation 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 three 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 sensitisation 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 two 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 sensitisation of 38.2% correlates well to other similar cohorts,^{29 31} and this together with the large study sample and settings of the PreventADALL indicates that the generalizability is adequate and the results reproducible in other cohorts with similar settings.

Clinical implication and future research

At three months of age, less than 30% of food extract sensitised 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 sensitisation and maternal food sensitisation 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 risk³⁶ or in observational studies,³⁷ 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.^{38,39} The general population-based PreventADALL study will be further explored for the possible impact of early complementary food introduction to reduce food allergy in sensitised and non-sensitised infants.

Conclusion

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

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TABLES

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)	
Study country (N=1110/2396)	n	% (95 % CI)	n	% (95 % CI)	n	% (95 % CI)
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)
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Table 2. Maternal and perinatal factors associated with any infant sensitisation at 3 months of age (inhalant or food specific IgE ≥ 0.1 kU_A/L) N=79

	<i>n/N (%)</i>	<i>Crude OR (95% CI)</i>	<i>Adjusted* OR (95% CI)</i>
Offspring gender (ref female)	492/1104 (44.6)	0.60 (0.41-1.07)	0.68 (0.40-1.13)
Maternal sensitisation (any, ≥ 0.35 kU _A /L)	399/1065 (37.4)	1.42 (0.88-2.28)	1.13 (0.66-1.94)
Maternal food sensitisation (any, ≥ 0.35 kU _A /L)	44/1068 (4.1)	3.67 (1.69-7.96)	3.64 (1.53-8.68)
Maternal inhalant sensitisation (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 w)	131/1086 (12.1)	0.69 (0.31-1.54)	
Low birth weight (<2500g)	16/1098 (1.4)	3.05 (0.85-10.95)	3.59 (0.70-18.38)

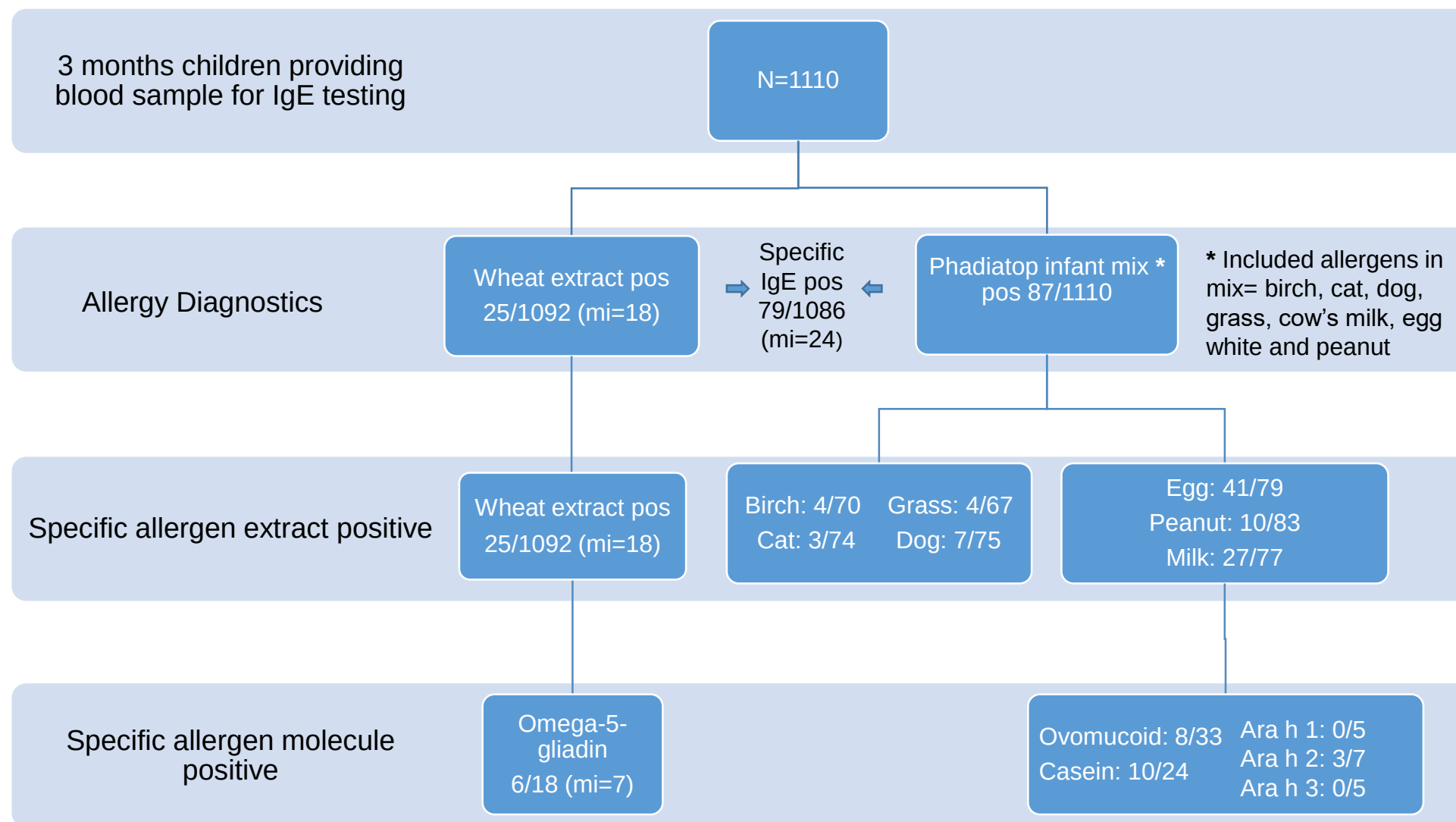
* adjusted for variables with association p-values of 0.2 or less in the univariate analyses: infant gender, pet at home, low birth weight, maternal sensitisation, maternal food sensitisation. rDD= self-reported doctor diagnose. PN= vaginal delivery

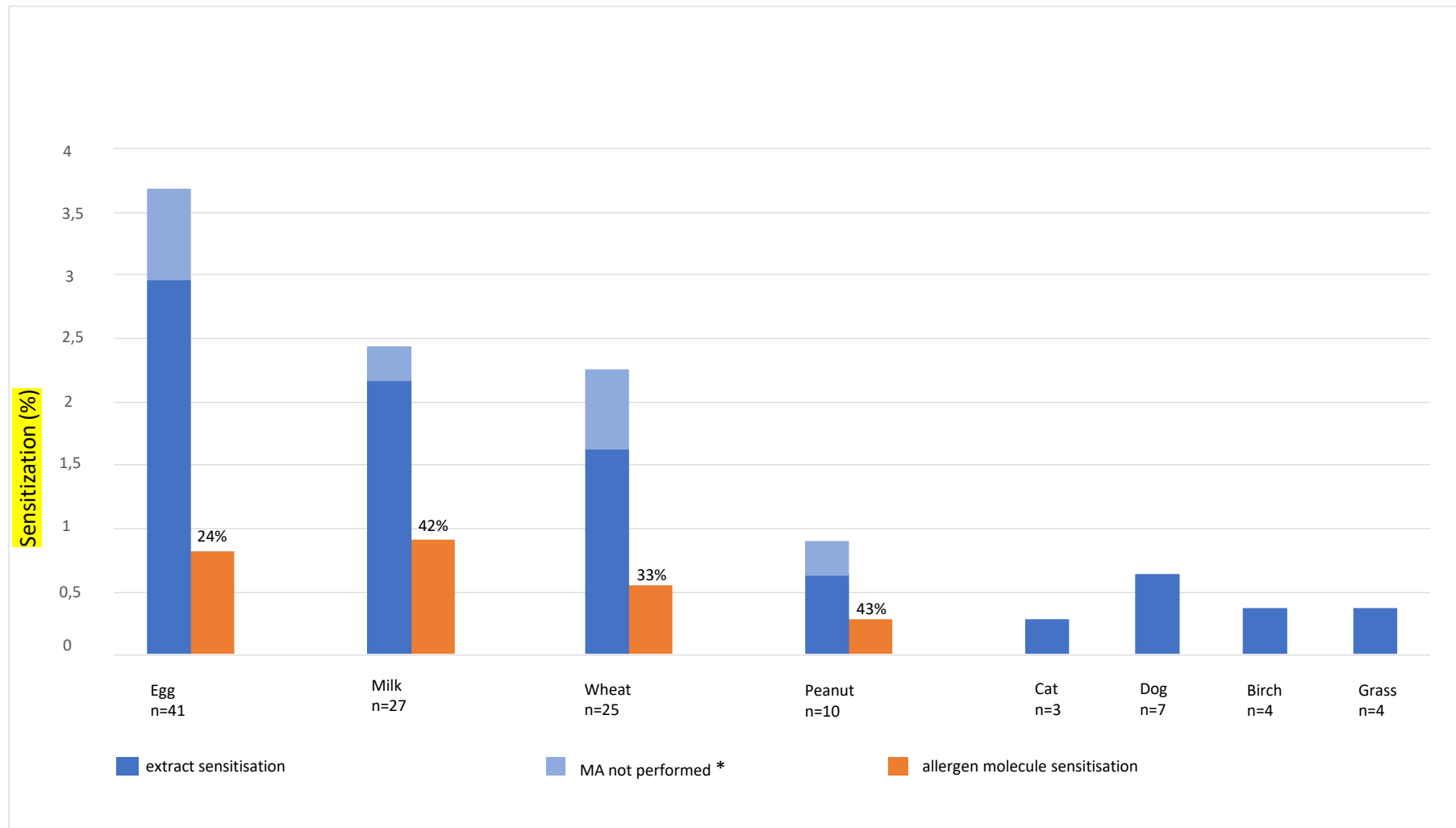
FIGURE LEGENDS

FIG 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).

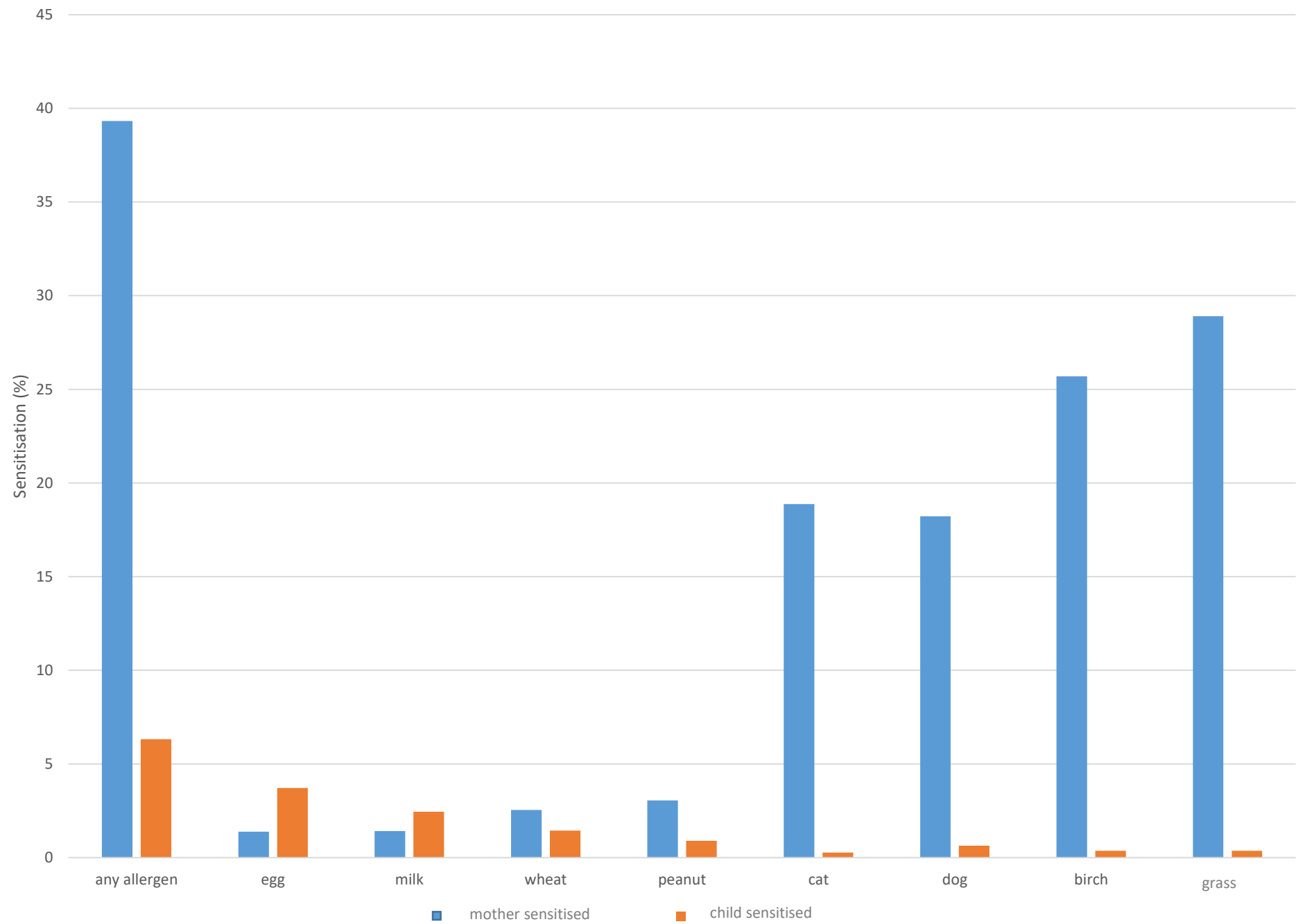
FIG 2. Specific IgE sensitisation (≥ 0.1 kU_A/L) prevalence in children 3 months of age (%) N=79 and co-existing allergen molecule sensitisation, MA=missing allergen, no analysis made for allergen molecules due to lack of sera.

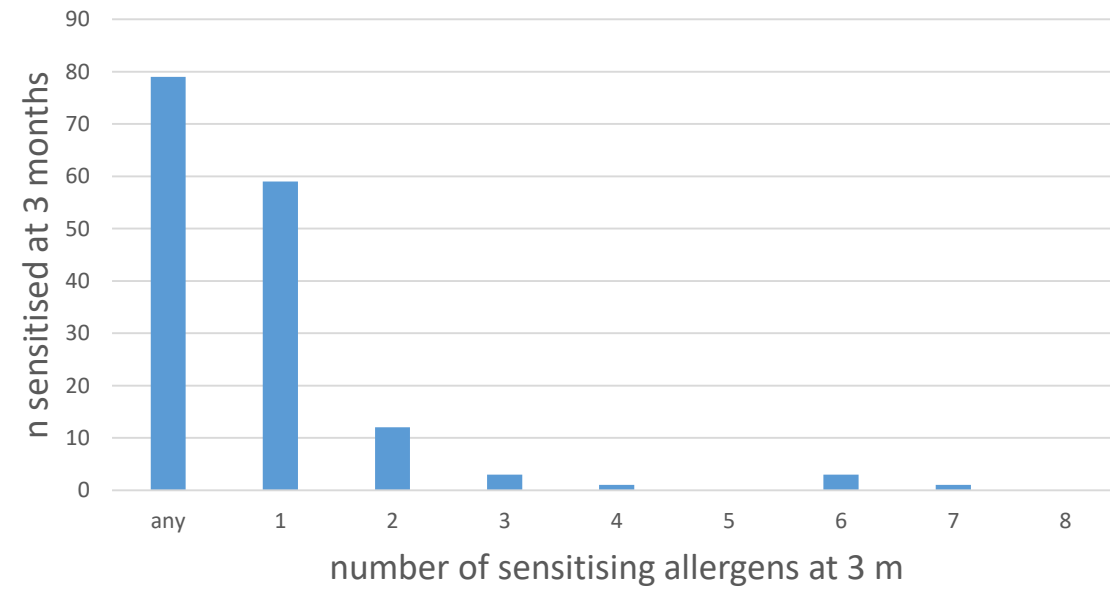
FIG 3. Specific IgE sensitisation prevalence among pregnant women (≥ 0.35 kU_A/L) and children (≥ 0.1 kU_A/L) at 3 months of age, N=1100, (%).

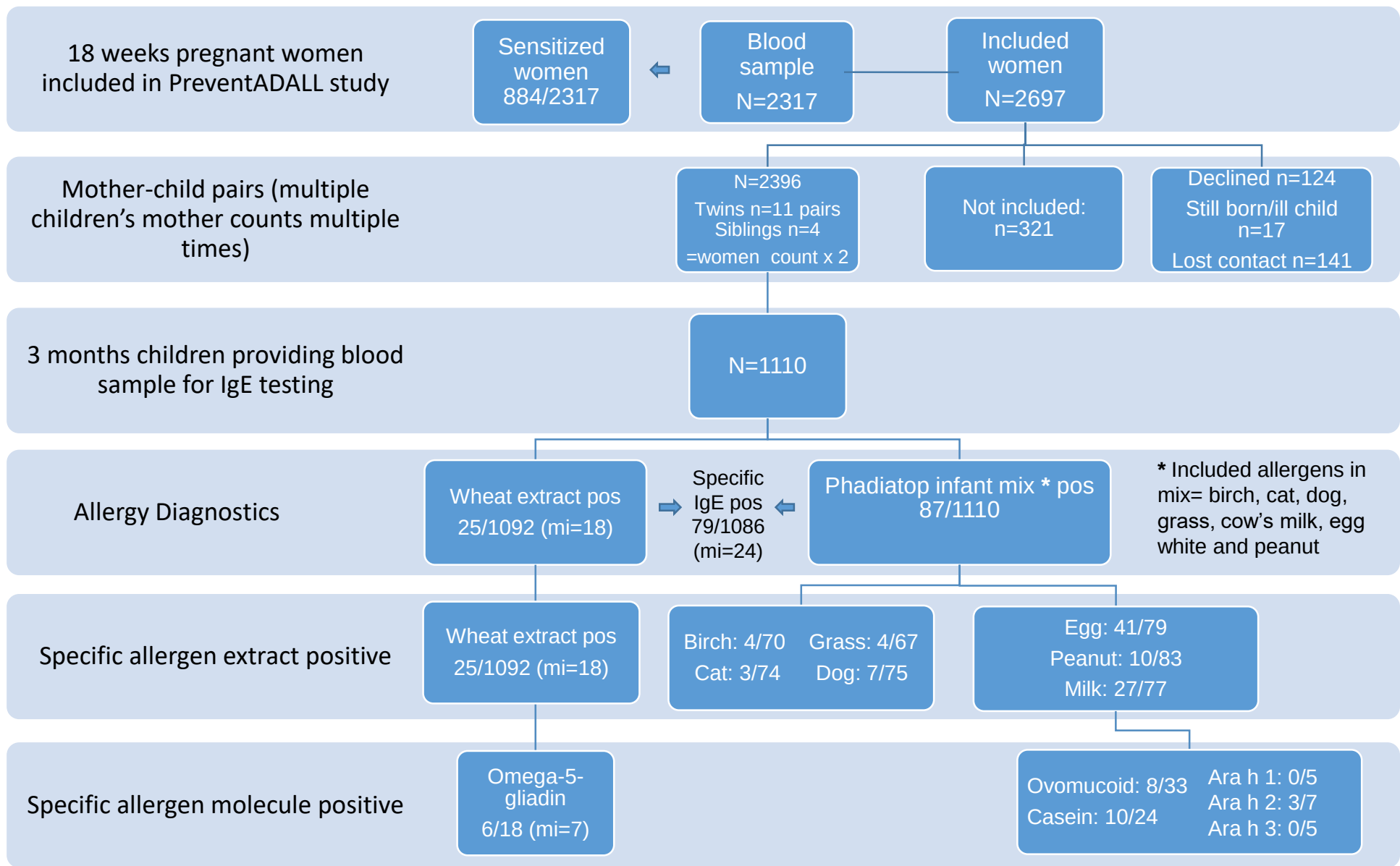


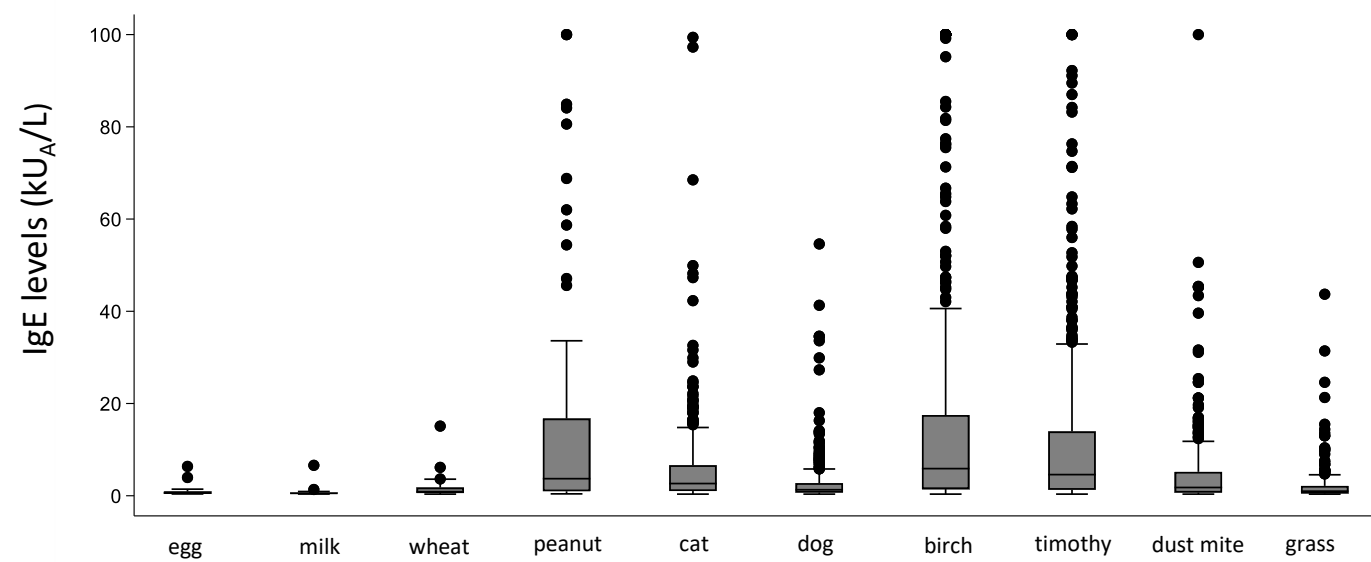
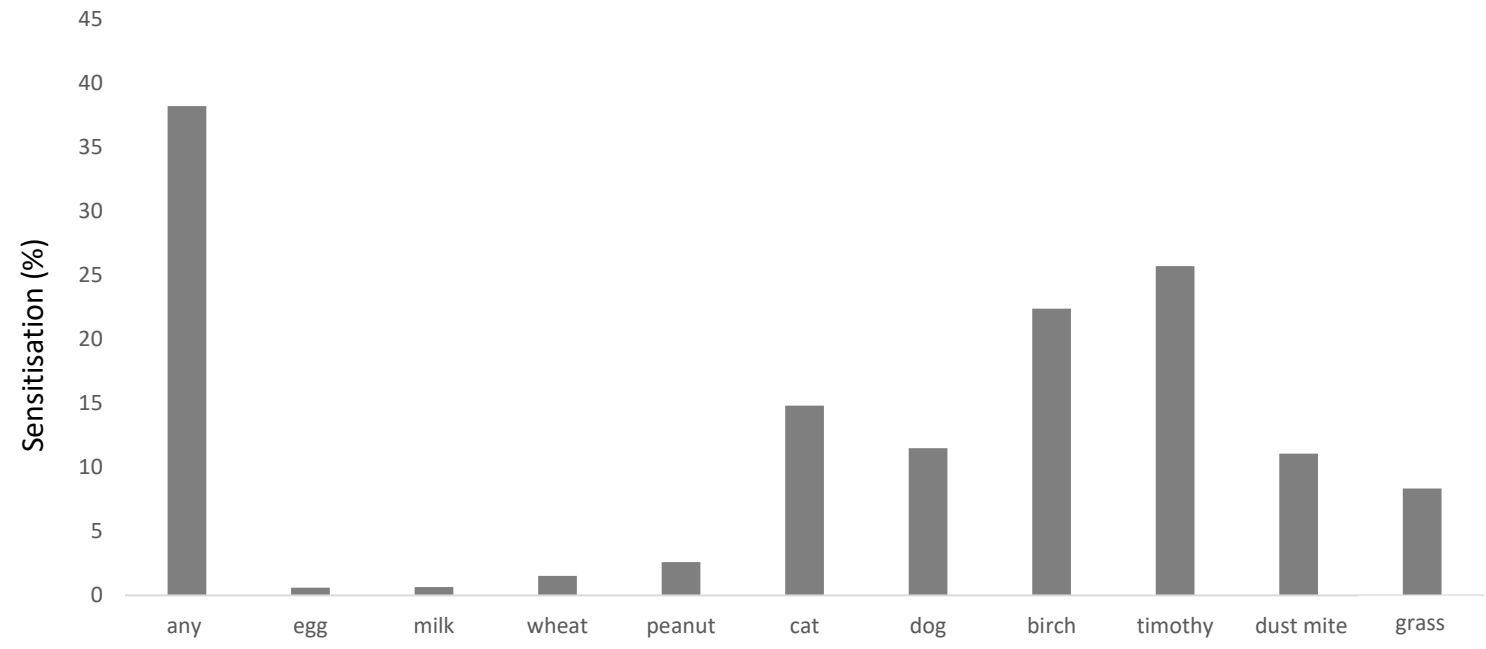


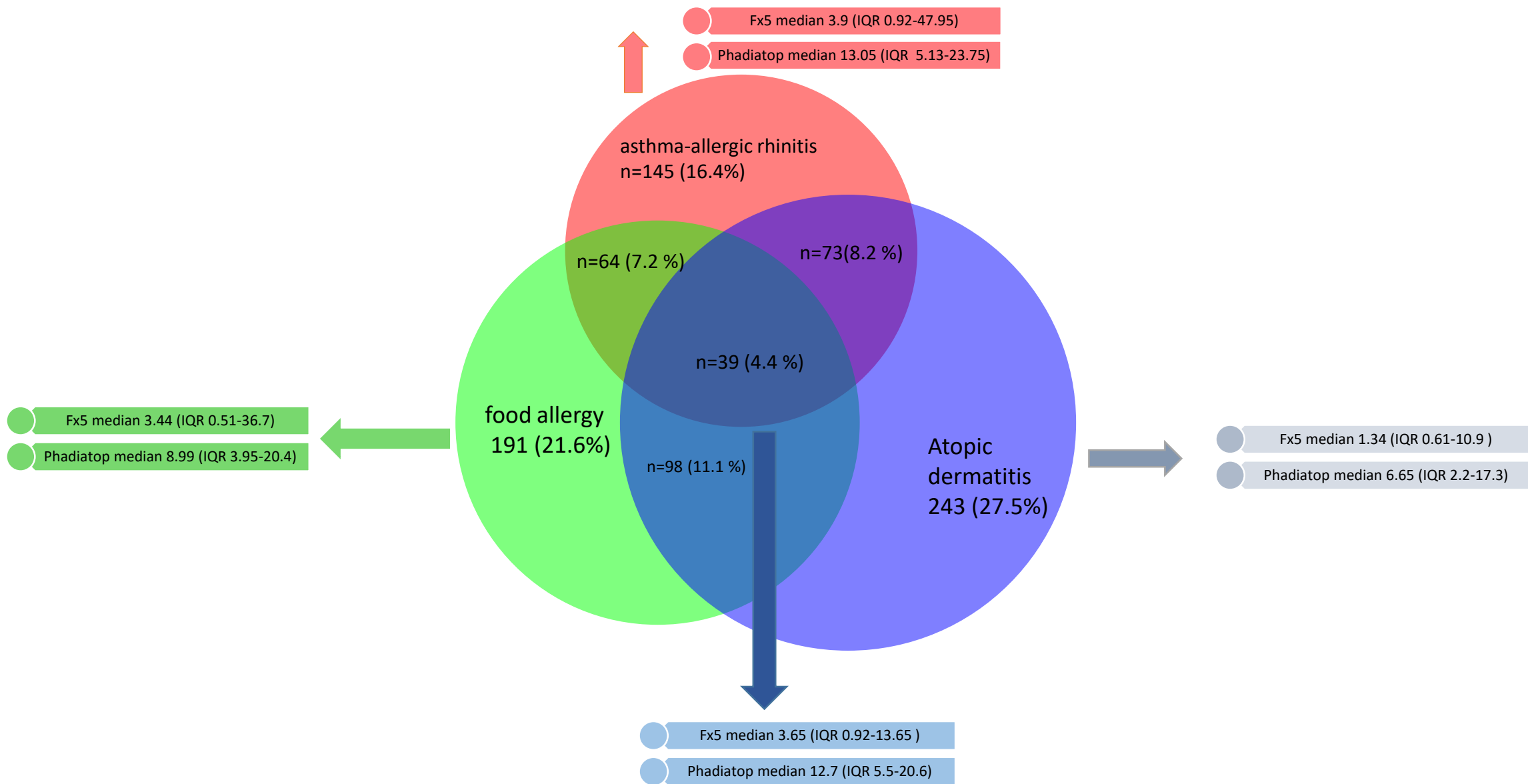
* MA=molecular allergology not performed, no analysis made for allergen molecules due to lack of sera



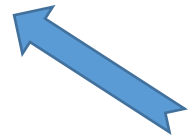




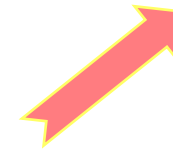
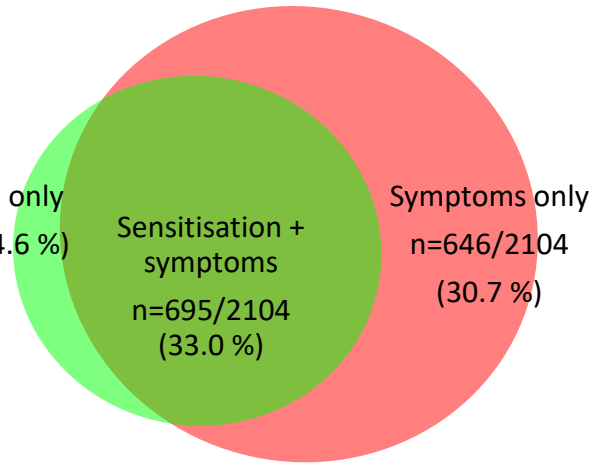




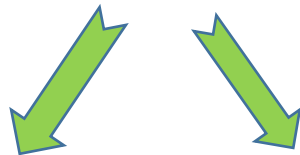
Phadiatop median IgE 1.56 kU_A/L (IQR 0.67-4.02)
Fx5 foodpanel median IgE 0.69 kU_A/L (range 0.41-1.22)



Sensitisation only
n=98/2104 (4.6 %)

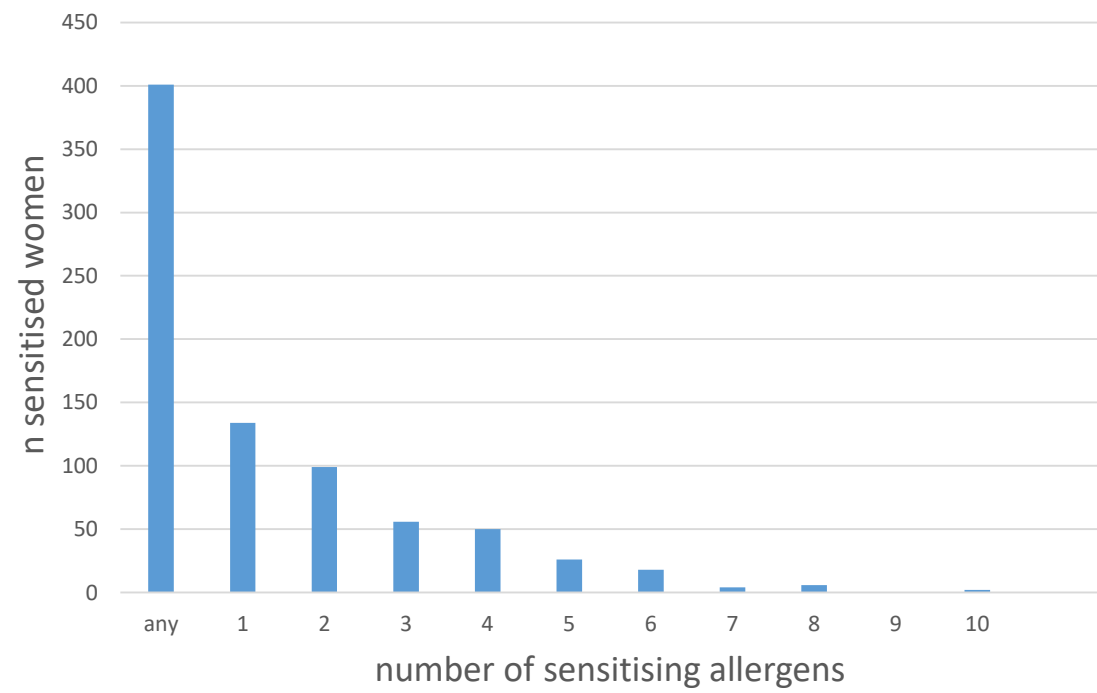


Asthma 131/646 (20.3 %)
Rhinitis 64/646 (9.9 %)
Atopic dermatitis 175/646 (27.1 %)
Food allergy 84/646 (13.0 %)



Phadiatop median IgE 6.41 kU_A/L (IQR 2.58-15.6)
Fx5 food panel median IgE 1.34 kU_A/L (IQR 0.5-13)

Astma 226/695 (32.5 %)
Rhinitis 367/695 (52.8 %)
Atopic dermatitis 243/695 (35.0 %)
Food allergy 191/695 (27.5 %)



1 ONLINE REPOSITORY

2 Extract and molecular-based early infant sensitisation and associated factors 3 – a PreventADALL study

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57 ONLINE REPOSITORY RESULTS

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59 Maternal sensitisation

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61 General characteristics on background factors and reported allergic diseases of the women are
62 presented in Supplement Table S1. Comparison to the whole cohort is available in Supplement Table
63 S2. Among the 2317 women with available IgE data at mid-pregnancy, 884 (38.2%) were sensitised to
64 at least one inhalant or food allergen. The most common inhalant sensitisation was against grass, in
65 593 women (25.7%), closely followed by birch in 518 (22.4%), Supplement Fig S3. Most common
66 maternal food sensitisation was against peanut, found in 60 women (2.6%), followed by wheat in 35
67 (1.5%). Spread of specific IgE levels are also shown in Fig S3.

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69 Among the 2169 with available data on maternal atopic disease, doctor diagnose of asthma was self-
70 reported in 371 women (17.1%), allergic rhinitis in 445 women (20.5%), atopic dermatitis in 431
71 (19.8%), and food allergy in 281 (12.9%), Supplement Table S2. Details regarding sensitised women
72 simultaneously reporting symptoms of asthma and rhinitis, eczema and food allergy are presented in
73 Supplement Fig S4. Among the 884 sensitised women 39 (4.4%) reported all four allergic symptoms.
74 However, some women reported atopic disease without being sensitised, Supplement Fig S5.
75 Polysensitisation of two or more allergens were found in 24.5% of the women, see Supplement Fig S6.

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80 **Supplement S1. Infant sensitisation prevalence**

	n	% (95 % CI)
Any sensitisation(N=1086)	79	7.3 (5.8-8.8)
Monosensitisation	59	75
Polysensitisation (2 allergens)	20	25
Polysensitisation (3 or more)	8	10
Egg (N=1102)	41	3.7 (2.7-5.0)
Milk(N=1100)	27	2.5 (1.6-3.5)
Peanut (N=1106)	10	0.9 (0.4-1.6)
Wheat (N=1092)	25	2.3 (1.5-3.4)
Birch (N=1093)	4	0.4 (0.0-0.9)
Grass (N=1090)	4	0.4 (0.1-0.9)
Cat (N=1097)	3	0.3 (0.0-0.8)
Dog (N=1098)	7	0.6 (0.2-1.3)
Ovomukoid(N=1056)	9	0.8 (0.4-1.6)
Casein (N=1047)	10	0.9 (0.4-1.7)
Ara h 1 (N=1027)	0	0
Ara h2 (N=1030)	3	0.3 (0.0-0.8)
Ara h 3 (N=1028)	0	0
Omega 5 gliadin (N=1036)	6	0.5 (0.2-1.2)

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83 **Table S2. General characteristics women N=2317, n (%)**

	n	% (95 % CI)
Study country (N=2321)		
Norway	1817	78.3 (76.0-80.0)
Sweden	504	21.7 (20.0-23.4)
Mother's first child (N=1157)	837	72.3 (70.0–75.0)
Maternal BMI (N=2283)		
>25	885	38.8 (37.0–41.0)
>30	204	8.9 (8.0–10.0)
Low maternal age (<25) (N=2321)	56	2.4 (2.0–3.0)
Low maternal education (N=2097) (primary school/high school)	231	11.0 (10.0-12.0)
Low maternal income (< 300 000 NOK/ per year) (N=2321)	24	1.03 (1.0–2.0)
Furry pet at home (N=2108)	496	23.5 (21.0–25.0)
Maternal smoking (N=2107)	574	27.2 (25.0–29.0)
Maternal atopic dermatitis, reported doctor diagnosed (N=2108)	419	19.9 (18.0–22.0)
Maternal asthma, reported doctor diagnosed (N=2108)	358	17.0 (15.0–19.0)
Maternal allergic rhinitis, reported doctor diagnosed (N=2108)	433	20.5 (18.8-22.3)
Maternal food allergy, reported doctor diagnosed (N=2108)	275	13.0 (13.08 11.6-14.5)

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Table S3. Comparison of general characteristics, all included mother-infant pairs in PreventADALL cohort (N=2396) vs study group consisting of mother-child-pairs with IgE-data available (N=1110).

	Mothers-Child pairs N=2396		Study group N= 1110	
	n	% (95% CI)	n	% (95% CI)
Study country (N=2396/1110)				
Norway	1879	78.4 (76.7-80.0)	806	72.6 (69.9-75.2)
Sweden	517	21.6 (18.1-25.1)	304	27.4 (22.4-32.4)
Child male sex (N=2396/1110)	1258	52.5 (49.7-55.3)	616	55.5 (51.6-59.4)
Mother's first child (N=2172/1010)	1308	60.2 (58.1-62.3)	598	59.2 (56.1-62.2)
Maternal BMI (N=2355/1096)				
>25	916	38.9 (36.9-40.9)	424	38.7 (35.8-41.6)
>30	213	9.0 (7.9-10.3)	96	8.8 (7.2-10.6)
Low maternal age (<25) (N=2165)	59	2.5 (0-6.5)	27	2.4 (0-8.2)
Low maternal education (primary school/high school) (N=2161/1004)	239	11.1 (9.8-12.5)	101	10.1 (8.3-12.1)
Low maternal income (< 300 000 NOK/ per month)	339	15.6 (14.1-17.2)	155	15.4 (13.2-17.7)
Furry pet at home (N=2172/1010)	513	23.6 (21.8-25.5)	232	23.0 (20.4-25.7)
Maternal smoking (N=2171/1009)	590	27.2 (25.3-29.1)	274	27.2 (24.4-30.0)
Maternal atopic dermatitis, doctordiagnosed (N=2172/1010)	431	19.8 (18.2-21.6)	185	18.3 (16.0-20.8)
Maternal asthma doctordiagnosed (N=2172/1010)	371	17.1 (15.5-18.7)	166	16.4 (14.2-18.9)
Maternal allergic rhinitis, doctordiagnosed (N=2172/1010)	445	20.5 (18.8-22.2)	208	10.3 (13.3-24.2)
Maternal food allergy, doctordiagnosed (N=2172/1010)	281	12.9 (11.6-14.4)	129	12.8 (10.8-15.0)

95 **ONLINE REPOSITORY FIGURE LEGENDS**

96

97 Supplement FIG S1. Any sensitisation and polysensitisation in children 3 months, N =79, cut-off 0.10
98 kU/L

99 Supplement FIG S2. Flow chart whole cohort.

100 Supplement FIG S3. Percentage of pregnant women with allergen-specific sensitisation at 18 weeks
101 gestation, and spread of specific IgE-levels, N=2317 (%) and spread of IgE levels (kU_A/L)

102 Supplement FIG S4. Reported doctor-diagnosed allergic disease among sensitised pregnant women,
103 N=884, IgE levels in

104 Supplement FIG S5. Sensitised vs non-sensitised 18 week pregnant women with/without self-reported
105 doctor diagnose of allergic symptoms (asthma, rhinitis, atopic dermatitis and/or food allergy) , N=2104

106 Supplement FIG S6. Allergen polysensitisation in women 18 weeks of gestation, N=1110, cut-off
107 0.35kU_A/L

108

109

110