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Maternal allergen-specific IgG might protect the child against allergic sensitization

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Abstract

Background—Analysis of allergen-specific IgE responses in birth cohorts with microarrayed allergens has provided detailed information regarding the evolution of specific IgE responses in children. High-resolution data regarding early development of allergen-specific IgG are needed.

Objective—We sought to analyze IgG reactivity to microarrayed allergens in mothers during pregnancy, in cord blood samples, in breast milk, and in infants in the first years of life with the aim to investigate whether maternal allergen-specific IgG can protect against IgE sensitization in the offspring.

Methods—Plasma samples from mothers during the third trimester, cord blood, breast milk collected 2 months after delivery, and plasma samples from children at 6, 12, and 60 months of age were analyzed for IgG reactivity to 164 microarrayed allergens (ImmunoCAP ISAC technology) in 99 families of the Swedish birth cohort Assessment of Lifestyle and Allergic Disease During Infancy (ALADDIN). IgE sensitizations to microarrayed allergens were determined at 5 years of age in the children.

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Results—Allergen-specific IgG reactivity profiles in mothers, cord blood, and breast milk were highly correlated. Maternal allergen-specific IgG persisted in some children at 6 months. Children's allergen-specific IgG production occurred at 6 months and reflected allergen exposure. Children who were IgE sensitized against an allergen at 5 years of age had significantly higher allergen-specific IgG levels than nonsensitized children. For all 164 tested allergens, children from mothers with increased (>30 ISAC standardized units) specific plasma IgG levels against an allergen had no IgE sensitizations against that allergen at 5 years of age.

Conclusion—This is the first detailed analysis of the molecular IgG recognition profile in mothers and their children in early life. High allergen-specific IgG reactivity in the mother's plasma and breast milk and in cord blood seemed to protect against allergic sensitization at 5 years of age.

Keywords

Allergy; allergen; allergen-specific IgG; birth cohort; breast milk; cord blood; maternal IgG; microarrayed allergens; recombinant allergen; sensitization

Birth cohort studies have shown that allergic sensitization develops early in childhood, beginning with IgE sensitization to food allergens and followed by sensitization to respiratory allergens.1,2 With the introduction of molecular allergy diagnosis based on recombinant allergens, it has become possible to decipher IgE reactivity profiles against individual allergen molecules.3–5 In fact, the use of allergen chips containing comprehensive panels of microarrayed allergen molecules allows detailed investigation of the evolution of specific IgE responses to a large number of allergen molecules with small amounts of serum, and thus this technology has opened the door for multiplex IgE serology in children.6 The development of allergen-specific IgE responses during childhood has been investigated in several European birth cohorts, especially within the European Union–funded research project Mechanisms of the Development of Allergy (MeDALL).7

For most children, it has been shown that IgE sensitization to food and respiratory allergens starts in the first few years of life with the recognition of major allergens.8–12 Interestingly, it seems to be possible to predict whether a child will have symptoms later in life and the severity of those symptoms based on IgE reactivity profiles (ie, allergen-specific IgE levels, numbers of recognized cross-reactive allergens, and numbers of allergen molecules from the same allergen source) measured in not yet symptomatic children early in life.8,10 Most of the children maintain their early acquired IgE sensitization profiles, but there are also children who continue to acquire sensitizations to additional allergens, as demonstrated by IgE seroconversion, until puberty and sometimes adolescence.8–11 A study that analyzed adult allergic patients regarding their molecular IgE reactivity profiles for a period of 10 years has shown that in adulthood the established IgE sensitizations remain unaltered.13 Thus the first years in the life of children seem to represent a period of plasticity of the atopic immune system during which IgE sensitizations occur or at least become detectable.14

Microarrayed allergens are being used increasingly for allergy diagnosis to resolve complex polysensitization15 and for the monitoring of the development of allergen-specific IgE

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responses in childhood, but the technology has been used much less for studying allergen-specific IgG responses. In fact, only a few studies have performed a microarray analysis of allergen-specific IgG responses in allergic patients to understand mechanisms of class-switching toward IgE production,16 to analyze allergen-specific IgG responses in clinically well-defined populations to understand mechanisms of allergen-specific IgG production, 17,18 and to monitor the development of allergen-specific blocking IgG antibodies during allergen-specific immunotherapy (AIT).19,20 For AIT, it has been shown that induction of allergen-specific IgG antibodies is a major mechanism for successful AIT,21 and measurement of IgG antibodies blocking the IgE-allergen interaction is the basis for several biomarker assays used for monitoring AIT.22 In addition, several studies indicate a possible beneficial role of “natural” allergen-specific IgG responses.23–25

Several experimental studies conducted in rats and mice have even indicated that maternal allergen-specific IgG transmitted to the offspring can prevent the development of allergic sensitization.26–29 To investigate in detail the transition of maternal allergen-specific IgG antibodies from mothers to their children and the development of allergen-specific IgG antibodies in infancy, we used microarray technology to measure levels of IgG antibodies to 164 different allergen molecules. The analyses were conducted in the Assessment of Lifestyle and Allergic Disease During Infancy (ALADDIN) cohort30 in which blood samples of mothers close to delivery, cord blood samples, breast milk samples, and blood from children obtained at 6 months, 12 months, and 5 years after birth were available to allow capturing the mother-to-child transition of maternal allergen-specific IgG and the beginning of allergen-specific IgG production in the infant. In addition, development of allergen-specific IgE reactivity in children was measured against the same 164 allergens to study whether maternal allergen-specific IgG antibodies can protect against allergic sensitization.

Methods

Study population

The ALADDIN study population was recruited between September 2004 and November 2007 at anthroposophic and conventional maternal health care centers in the area around Stockholm, Sweden. Classification of the participating families into lifestyle groups is described.30 In the present study mother/child pairs (n = 99) were included if plasma samples, cord blood samples, and blood samples from children obtained at the age of 6, 12, and 60 months were available. For 98 mother/child pairs, mature breast milk samples from mothers were also available. Demographic and clinical characteristics of the families are displayed in Table I. Plasma samples from the mothers were collected during the third trimester, cord blood samples were collected at birth, and breast milk samples were obtained 2 months after delivery. Furthermore, plasma had been collected from the infants at 6 months, 12 months, and 5 years of age. Allergen-specific IgE was analyzed in the parents and their children at 5 years of age by using Phadiatop (a mix of 11 inhalant allergen extracts) and for children also with fx5, a mix of 6 food allergen extracts (hen’s egg, cow’s milk, peanut, soy, cod, and wheat; both from Thermo Fisher Scientific, Uppsala, Sweden). Patients were classified as sensitized if the IgE level was 0.35 kU_A/L or higher. The study

was approved by the local ethics committee in Stockholm, Sweden (Dnr 474/01, 07-01-2002 and Dnr 329-32, 21-02-2012). Written informed consent was obtained from all parents. Anonymized samples were analyzed with approval of the Ethics Committee of the Medical University of Vienna (EK1641/2014).

Determination of allergen-specific IgG and IgE levels using microarrayed allergens

Blood samples were collected in sodium heparin tubes, and plasma was separated and stored at −20°C. Breast milk samples were collected 2 months after delivery, kept at 4°C until frozen within 24 hours, and stored at −80°C. Allergen-specific IgG and IgE levels toward 164 purified natural and recombinant allergens representing 48 allergen sources were measured with a customized microarray based on the ImmunoCAP ISAC technology (ImmunoCAP ISAC customized version; Phadia AB, Uppsala, Sweden).6 The list of analyzed allergens is displayed in Table E1 in this article's Online Repository at www.jacionline.org. Allergen-specific IgE reactivities and levels were determined in undiluted plasma samples, as previously described.6,8 For detection of allergen-specific IgG, plasma samples were diluted 1:50 before analysis.6,17 Breast milk samples were centrifuged for 10 minutes at 2500*g* before use to remove lipids.31 Allergen-specific IgG in breast milk samples was detected, as previously described.31 Results were expressed in ISAC standardized units (IgE, ISU; IgG, ISU-G). Thresholds for IgE sensitization and IgG positivity were set to 0.3 ISU and 0.5 ISU-G, respectively.17

Statistical methods

Correlation coefficients were calculated by using the Spearman rank-order correlation test with SPSS Statistics 20 (IBM, Armonk, NY). Differences in allergen-specific IgG and IgE levels were analyzed by using the Wilcoxon–Mann–Whitney *U* test. Results with *P* values of .05 or less were considered statistically significant. Differences regarding categorical variables and continuous variables in Table I were calculated by using Fisher exact and Kruskal-Wallis tests, respectively.

Results

Blood and breast milk samples from the ALADDIN cohort allow analysis of mother-to-child transmission of allergen-specific IgG and early evolution of children's IgE and IgG responses

A major feature of the ALADDIN birth cohort is that blood samples were obtained from children during early infancy (ie, at 6 months, 12 months, 24 months, and 5 years of age) together with blood samples from their parents, cord blood samples, and breast milk samples. Thus it was possible to compare IgE and IgG reactivity against a large number of allergen molecules in blood and breast milk of the mothers with reactivity profiles in cord blood and in blood samples of children within their first years of life and in particular at 6 and 12 months after birth. In this study we analyzed 99 families (ie, mother and child) for whom a complete set of blood samples was available. Twenty-two families had an anthroposophic lifestyle characterized by a high prevalence of vegetarian diet, home delivery, and prolonged breast-feeding30; 42 families had a partly anthroposophic and 35

had a nonanthroposophic lifestyle (Table I). Of the 99 children, 54 were female, and 45 were male, and all were born full-term (gestational weeks 36-42).

IgE testing with microarrayed allergen molecules is more sensitive in detecting IgE sensitization than traditional allergen extract–based serology

Analysis of IgE sensitizations in children at age 5 years was performed by using traditional allergen extract–based IgE serology (ie, Phadiatop and fx5) and by using a panel of 164 microarrayed allergen molecules, as described by Lupinek et al (see Table E1).6 Twenty-nine mothers, 38 fathers, and, at 5 years of age, 33 children were IgE sensitized according to traditional allergen extract–based IgE serology, Phadiatop measurements, and also fx5 measurements for children (Table I). We found that the panel of microarrayed allergen molecules was more sensitive in detecting IgE sensitizations in the 99 children at age 5 years than traditional allergen extract–based serology, identifying 43% and 33% sensitized children, respectively (Fig 1).

A comparison of IgE sensitization rates (ie, positivity to ≥1 of the microarrayed allergens [≥0.3 ISU]) in families with different lifestyles showed that they were comparable in children from anthroposophic families (ie, 41% sensitized) and children from partly anthroposophic (ie, 45%) and nonanthroposophic (ie, 43%) families. However, we noted that the proportion of children from the anthroposophic group who had an IgE sensitization to food allergen extracts was smaller than in the nonanthroposophic children, but this did not reach significance in the 99 families investigated in this study (Table I).

Frequencies of IgE sensitizations to the individual allergens found in all 99 children are displayed in Table II. Omitting subsequent cross-reactive allergens in the list, the most frequently detected allergens were the major timothy grass pollen allergen Phl p 1 (19%), the major birch pollen allergen Bet v 1 (10%), the major wasp allergen Ves v 5 (10%), and the major cat allergen Fel d 1 (6%). This molecular IgE sensitization profile was very similar to the profiles found in other Scandinavian birth cohorts.8,10,32,33

Correlation of molecular IgG reactivity profiles in mother's blood, breast milk, and cord blood and in infants up to 6 months

First, we correlated allergen-specific IgG responses determined for the 164 allergen molecules in the blood and breast milk of mothers with those measured in cord blood and blood samples obtained from children at different ages (ie, 6 months, 12 months, and 5 years; Fig 2 and Table III). Allergen-specific IgG responses in blood samples from mothers and in corresponding cord blood samples were strongly correlated (r_S = 0.826; Fig 2, *A*, and Table III). The Spearman correlation coefficient of the IgG antibodies measured in blood of the mothers and their breast milk samples was lower (r_S = 0.647, Table III). When comparing allergen-specific IgG responses in the mothers with those found in blood samples from infants obtained at 6 and 12 months and from 5-year-old children, we found that the correlation was greatest for blood samples from infants obtained at 6 months (r_S = 0.522; Fig 2, *B*, and Table III) and disappeared at 12 months and 5 years (r_S = 0.360 and r_S = 0.431) of age (Fig 2, *C* and *D*, and Table III). These findings indicate that the allergen-recognition profile of the mothers in terms of specificities and levels is similar in cord blood and breast

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milk, as well as in the infants' blood at 6 months of age, whereas it differs from that found in blood samples obtained from children at a later time (ie, 12 months or 5 years) (see Fig E1 in this article's Online Repository at www.jacionline.org).

Children of mothers with high allergen-specific IgG levels lack IgE sensitization against that allergen at age 5 years

Associations of all allergen-specific IgE responses/levels in children at age 5 years with allergen-specific IgG responses/levels in mothers and cord blood are shown in Fig 3, *A* and *B*, respectively, for all 164 allergens. A total of 227 IgE reactivities at 5 years exceeded the threshold for IgE sensitization. Of 16,236 included maternal allergen-specific IgG values (99 families × 164 allergens), 352 values exceeded a threshold of 30 ISU-G (indicated by a vertical line in Fig 3, *A*). Table E2 in this article's Online Repository at www.jacionline.org shows that the data points in scatter plots from mother-child pairs with maternal IgG levels of 30 ISU-G or greater (Fig 3) are derived from a large number of pairs (n = 86) and include also a large number of allergens (see Fig E2 in this article's Online Repository at www.jacionline.org).

When only the 70 allergens with at least 1 child sensitized at 5 years are considered, 94 of 7425 maternal IgG values are greater than the threshold of 30 ISU-G. The allergens Fel d 1 and Gal d 1 featured several children with IgE levels of 0.3 ISU or greater and a substantial number of mothers with plasma IgG levels of greater than 30 ISU-G, whereas most allergens show either no or few maternal IgG values of greater than 30 ISU-G or no or few 5-year IgE values of 0.3 ISU or greater. Because each of these single components by themselves cannot be used to illustrate the existence of a maternal IgG threshold for child IgE sensitization for that specific allergen, all these allergens collectively contribute to the identification of a presumed "global" maternal IgG cutoff. In fact, when specific IgG levels toward an allergen in the mothers during the third trimester were greater than approximately 30 ISU-G, none of their children had allergen-specific IgE sensitizations of 0.3 ISU or greater at 5 years of age to that particular allergen (Fig 3, *A*, right). Allergen-specific IgE sensitizations were quite evenly distributed over the whole range of mothers' allergen-specific IgG levels of less than the cutoff level of approximately 30 ISU-G (see Fig E3, *A*, in this article's Online Repository at www.jacionline.org). This effect was found for children from both nonsensitized (ie, Phadiatop-negative) and sensitized (ie, Phadiatop-positive) mothers (see Fig E3, *B*). Likewise, when specific IgG levels against an allergen in cord blood exceeded a certain threshold (ie, 55 ISU-G), none of the children had an IgE sensitization of 0.3 ISU or greater at 5 years of age to that particular allergen (Fig 3, *B*, right). A similar cutoff for allergen-specific IgG was identified in cord blood of mothers in a birth cohort from another country (R. Valenta, unpublished data).

Transition of maternal allergen-specific IgG to infants and development of allergen-specific IgG production in infants

Fig 4 shows allergen-specific IgG levels in all samples from the mothers, cord blood, and samples from infants at the ages of 6 months, 12 months, and 5 years for frequently detected respiratory allergens (Fig 4, *A*: Phl p 1; Fig 4, *B*: Bet v 1; Fig 4, *C*: Fel d 1; and Fig 4, *D*: Can f 1), the wasp allergen Ves v 5 (Fig 4, *E*), and food allergens (Fig 4, *F*: Ara h 1; Fig 4,

G: Bos d 5; Fig 4, *H*: Gal d 1; and Fig 4, *I*: Tri a 36). Allergen-specific IgG levels in blood samples from the mothers and cord blood were always greater than those measured in children at 6 months of age. Thereafter, allergen-specific IgG levels increased in the infants at 12 months and in children at 5 years of age (Fig 4). Comparing allergen-specific IgG levels in infants and children at 6 months, 12 months, and 5 years of age, levels were greatest at 5 years for most allergens, except for Bos d 5 and Tri a 36, for which IgG levels were greater at 12 months compared with 5 years (Fig 4, *G* and *I*).

To analyze more closely maternal allergen-specific IgG reactivity profiles and those of the corresponding infants and children, we provide some examples for molecular IgG reactivity profiles measured for timothy grass pollen allergens (see Fig E1, *A*) birch pollen allergens (see Fig E1, *B*), Ves v 5 (see Fig E1, *C*), cat allergens (see Fig E1, *D*), and food allergens (Fig E1, *E*: peanut; Fig E1, *F*: egg; Fig E1, *G*: cow's milk; and Fig E1, *H*: wheat) in maternal, cord blood, and infant/children samples. There were several interesting observations: When we compared the profiles and intensities of allergen-specific IgG reactivity in blood samples from the mothers, cord blood, and breast milk, we found a good agreement regarding specificities and intensities for the individual tested allergens, which fits to the correlations found for all tested 164 allergens (Fig 2 and Table III).

In accordance with the fact that most of the children were not breast-fed any more at the age of 12 months (Table I) we noted a strong increase in cow's milk allergen–specific IgG antibody levels at the age of 12 months and thereafter, whereas they were still low at 6 months during breast-feeding (see Fig E1, *G*). Egg allergen-specific IgG responses were still low at 12 months of age but strongly increased at the age of 5 years, indicating a late introduction of egg into the diet (see Fig E1, *F*). Similar findings as for egg allergens were made for wheat allergens (see Fig E1, *H*).

In some infants it seemed that maternal allergen-specific IgG was still detectable at 6 months of age. For example, IgG specific for the allergens Phl p 1, Fel d 1, Ara h 1, and Gal d 3 in children from families b, e, i, and m (see Fig E1, *A*, *D*, *E*, and *F*, respectively) at the age of 6 months appeared to be derived from the mother because the infant's own IgG production became discernable from the mother's pattern later.

For most of the allergens, IgG levels were low at 6 months and increased strongly by age. Because mothers and children were obviously exposed to the same allergens, they had similar IgG antibody reactivities against most of the tested allergens, but there were also exceptions, such as the child from family p whose mother lacked relevant β-casein– and Bos d 8–specific IgG, although the child had a strong IgG response at 12 months of age against these allergens (see Fig E1, *G*).

IgE-sensitized children produce significantly more allergen-specific IgG than nonsensitized children

Fig 5 shows a comparison of IgG levels specific for the most frequently recognized allergens (Phl p 1, Bet v 1, Ves v 5, and Fel d 1) in blood samples from infants/children with and without sensitization to the given allergens at age 6 months, 12 months and 5 years. Interestingly, allergen-specific IgG levels in children at 5 years of age were significantly

greater in children who had an IgE sensitization against that allergen compared with nonsensitized children (Fig 5). In infants aged 6 and 12 months, IgG levels were much lower, and there were no significant differences between sensitized and nonsensitized children.

A detailed analysis of the allergen-specific IgG responses to the same allergens (ie, Phl p 1, Bet v 1, Ves v 5, and Fel d 1) according to the lifestyles of the families (see Fig E4 in this article's Online Repository at www.jacionline.org) shows that allergen-specific IgG responses were always greater in sensitized compared with nonsensitized children, regardless of lifestyle (Fig E4, left). Relevant allergen-specific IgE responses greater than the cutoff of 0.3 ISU were only detected in sensitized but not nonsensitized children (see Fig E4, right). Allergen-specific IgE levels were sometimes greater for children from families with a nonanthroposophic lifestyle and sometimes greater in children from families with an anthroposophic or partly anthroposophic lifestyle (see Fig E4).

Discussion

Our study is the first to perform a high-resolution analysis of specific IgG responses toward a comprehensive panel of 164 defined allergens from 48 allergen sources in samples from mothers, cord blood, and breast milk. In addition, transfer of maternal allergen-specific IgG to the offspring and development of allergen-specific IgG responses in the first year of life up to the age of 5 years, as well as the allergen-specific IgE reactivity profiles at 5 years, were analyzed. The detailed analysis was possible because in the ALADDIN cohort blood samples from mothers were obtained close to delivery. Cord blood and breast milk samples were available, and blood samples from the children were collected during infancy at the age of 6 or 12 months and from children at 5 years of age for a representative number of families (ie, n = 99). We found that allergen-specific IgG responses in the blood of mothers, cord blood, and breast milk were correlated and that profiles of maternal allergen-specific IgG reactivity could be detected in children, even up to the age of 6 months, although at low levels, which is in agreement with what is known about maternal transmission of gammaglobulins and their half-lives. An even more detailed analysis might have been obtained by the analysis of IgG subclass responses, but this was not performed in our study.

However, the major finding of our study was that children whose mothers had high levels of IgG antibodies against an allergen in their blood did not have allergic IgE sensitizations against this particular allergen. By contrast, only children whose mothers had lower allergen-specific IgG antibodies had IgE sensitization to allergens, which are commonly recognized by children in Scandinavia (ie, timothy grass [Phl p 1], birch [Bet v 1], wasp [Ves v 5], and cat [Fel d 1]).8,10,32,33 Similar results in terms of a "global maternal IgG cutoff" for IgE sensitization in the offspring have been obtained for a birth cohort from another country (R. Valenta, unpublished). The presumed global cutoff of maternal IgG of approximately 30 ISU-G applies for all 164 allergens tested in our study but might be lower for certain allergens. Depending on several factors, such as type of allergen, allergen exposure, maternal allergy, environmental conditions (eg, farm exposure), population investigated, and genetic predis-position maternal allergen-specific IgG cutoffs can also vary. In our study the protective effect of IgG was observed for both sensitized and

nonsensitized mothers. Farm exposure did not seem to play a major role because less than 10% of the mothers lived on farms during pregnancy.

The finding that children from mothers mounting high allergen-specific IgG levels did not have IgE sensitization is in agreement with a series of studies performed in different experimental animal models showing that offspring from mothers that produced high allergen-specific IgG levels could not be sensitized during the period when maternal IgG was present in the offspring because of immunization.26–29 Likewise, it has been demonstrated in several studies that administration of allergen-specific IgG antibodies to mice specifically conveyed protection against subsequent allergic sensitization against the allergen for which the specific antibodies had been administered.34–37 Thus it is likely that prevention of the development of allergic sensitization is directly mediated by allergen-specific IgG antibodies. Different mechanisms can be considered, such as simple neutralization of the allergen, thus preventing allergic sensitization through “antigen stealing” or targeting toward Fcγ receptor–containing immune cells, which removes the antigen, exhibits tolerogenic effects, or both.37

Interestingly, there is a study suggesting that AIT treatment of pregnant women can suppress the development of IgE sensitization against corresponding allergens in the offspring.38 Furthermore, it has been shown that AIT-induced allergen-specific IgG_1 and IgG_4 antibodies indeed cross the placenta and thus might be responsible for this effect.39 Therefore it is tempting to consider investigating in clinical studies whether induction of high levels of allergen-specific IgG antibodies in pregnant women by AIT can prevent allergic sensitization in the offspring.40 In fact, according to current guidelines, it is in principle possible to continue AIT during pregnancy,41 and there are currently safe forms of AIT being developed that could be suitable for such studies because of their greatly reduced allergenic activity.42–46

Because levels of maternal IgG antibodies transmitted to the child decrease and are already low at 6 months, it seems that the first months after birth define an important time window for allergic sensitization. In this context it has been reported that children born shortly before seasonal allergen exposure become preferentially sensitized toward these seasonal allergens.47

A second interesting finding of our study was that children with IgE sensitization against a particular allergen also had significantly greater allergen-specific IgG levels to the very same allergen as children without IgE sensitization (Fig 5). We have made similar observations in 2 other populations. In one study we measured allergen-specific IgE and IgG responses against a panel of house dust mite allergen molecules in more than 200 children25 and observed that children with IgE sensitization to house dust mite allergens had greater IgG levels to the very same allergens than children without IgE sensitization (see Fig 5 in Resch et al25).

Similar observations were also made in another cohort of 340 adult allergic subjects in whom we determined allergen-specific IgE and IgG responses.17 One explanation could be that allergen-specific antigen presentation in allergic subjects is regulated by HLA

background at the genetic level. In fact, associations of HLA types with IgE and IgG responses to certain allergens have been described by different authors and would explain why also allergen-specific IgG levels are increased in subjects with IgE sensitization, and a recent study suggests that genetic restriction of antigen presentation dictates allergic sensitization and allergen-specific antibody production.48–52

In summary, our study is the first to provide a detailed investigation of the transition of maternal allergen-specific IgG to the offspring and describes the evolution of allergen-specific IgG responses in infancy. It indicates that IgE-sensitized subjects are characterized also by production of greater allergen-specific IgG levels to the same allergen, which might be a result of a genetic predisposition at the level of HLA antigen presentation, increased T_H2 immunity, or both. Most importantly, our study provides strong evidence that high maternal allergen-specific IgG levels during pregnancy protect against allergic sensitization in the offspring, which might open new avenues for the prevention of allergic diseases.

Clinical implications: High levels of allergen-specific IgG in mothers during the third trimester and in cord blood seem to protect against allergic sensitization in offspring. This finding has implications for allergy prevention.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Abbreviations used

AIT	Allergen-specific immunotherapy
ALADDIN	Assessment of Lifestyle and Allergic Disease During Infancy
ISU	ISAC standardized units

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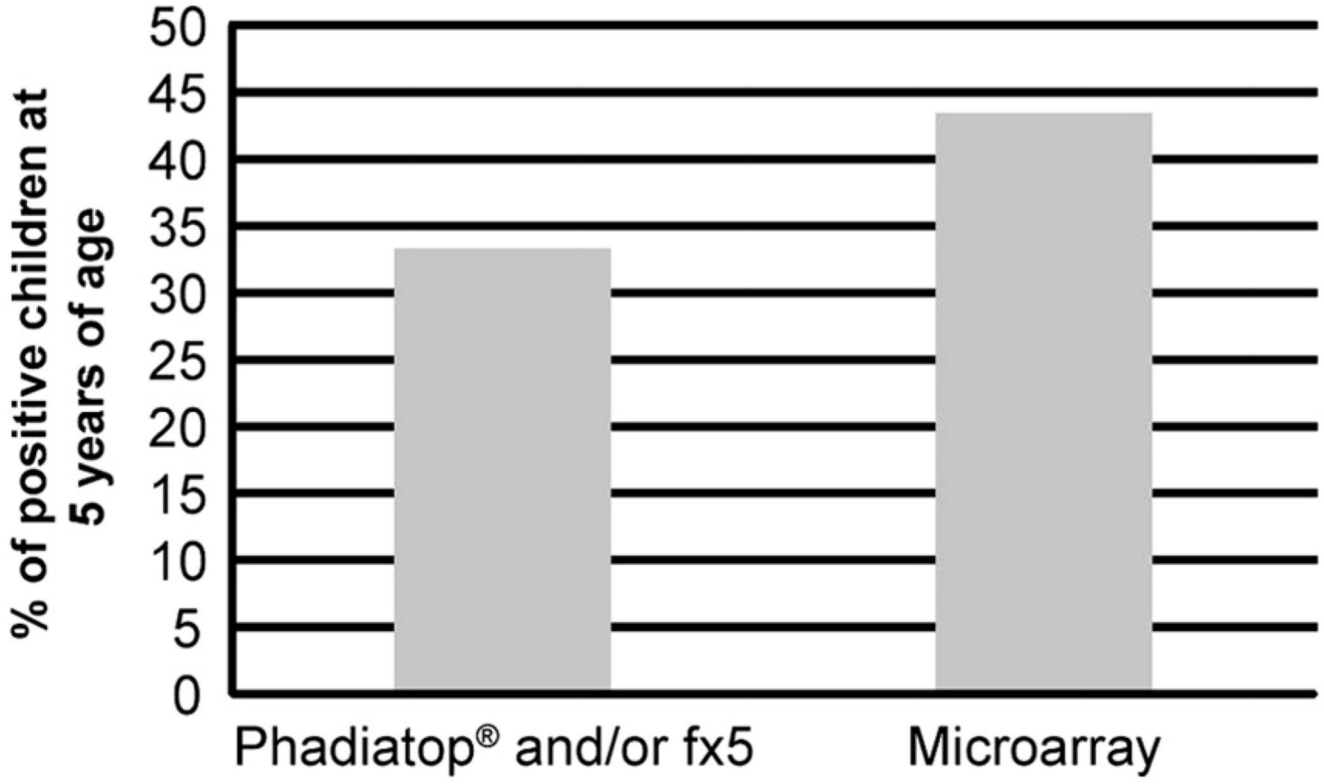

Fig 1.

Percentages of IgE-sensitized children (n = 99) at 5 years of age, as detected by means of allergen extract-based Phadiatop and fx5 testing, classified as sensitized if the IgE level was 0.35 kU_A/L or greater and, as detected by testing with the panel of microarrayed allergen molecules, classified as sensitized at 0.3 ISU or greater.

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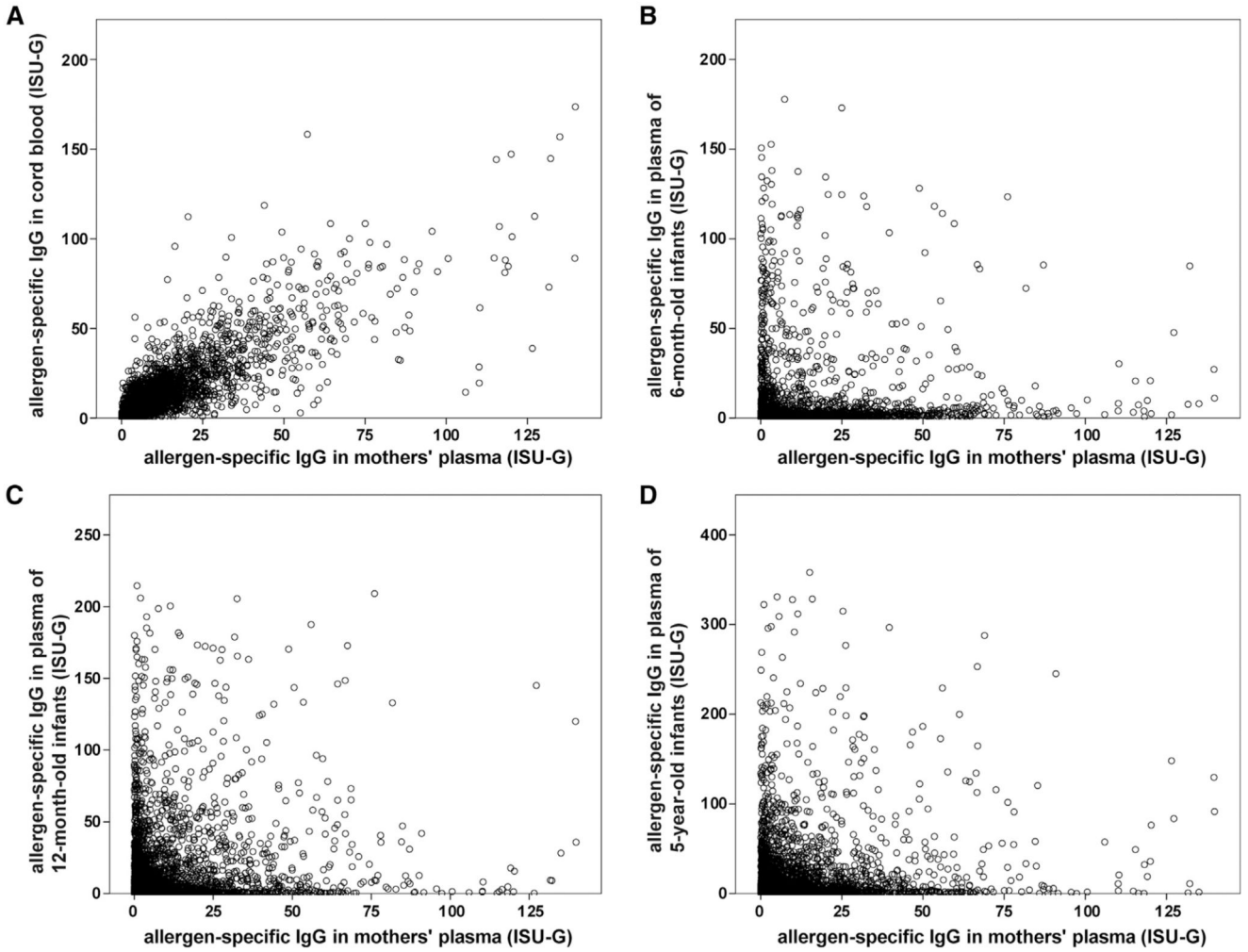

Fig 2.

Correlations between allergen-specific IgG levels (ISU-G) to each of the 164 microarrayed allergens in plasma samples of 99 mothers during the third trimester and corresponding plasma samples from their children at birth (cord blood) and 6 months, 12 months, and 5 years of age. Correlations of IgG levels in mothers with cord blood IgG (**A**), with IgG in children at 6 months (**B**), with IgG in children at 12 months (**C**), and with IgG in children at 5 years (**D**) are shown. Each *dot* is the IgG response to 1 allergen. Correlations are listed in Table III.

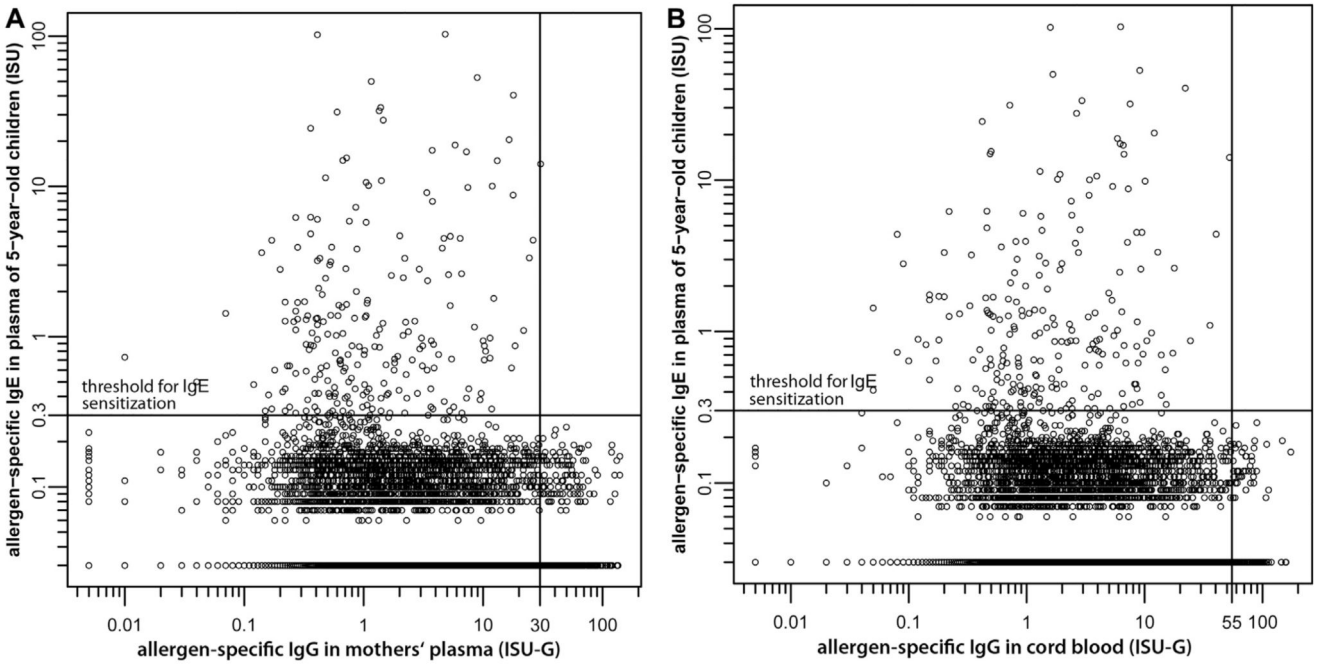

Fig 3.

Correlations between IgE levels (*y-axes*, ISU) specific for 164 microarrayed allergens in 99 children at the age of 5 years with allergen-specific IgG in maternal plasma (**A**) and with allergen-specific IgG in cord blood samples (**B**; *x-axes*, ISU-G) are shown. Each data point represents a pair of maternal/cord blood IgG and corresponding children's IgE levels at 5 years for 1 allergen. Each plot contains 99 families × 164 allergens = 16,236 data points. *Vertical lines* denote the observed cutoff of maternal allergen-specific IgG levels for the development of allergen-specific IgE sensitization. *Horizontal lines* indicate the threshold for IgE sensitization (≥0.3 ISU). All IgG and IgE levels of 0 ISU were substituted by a small value (IgE, 0.03; IgG, 0.005) to retain these data points in the figure on a logarithmic scale.

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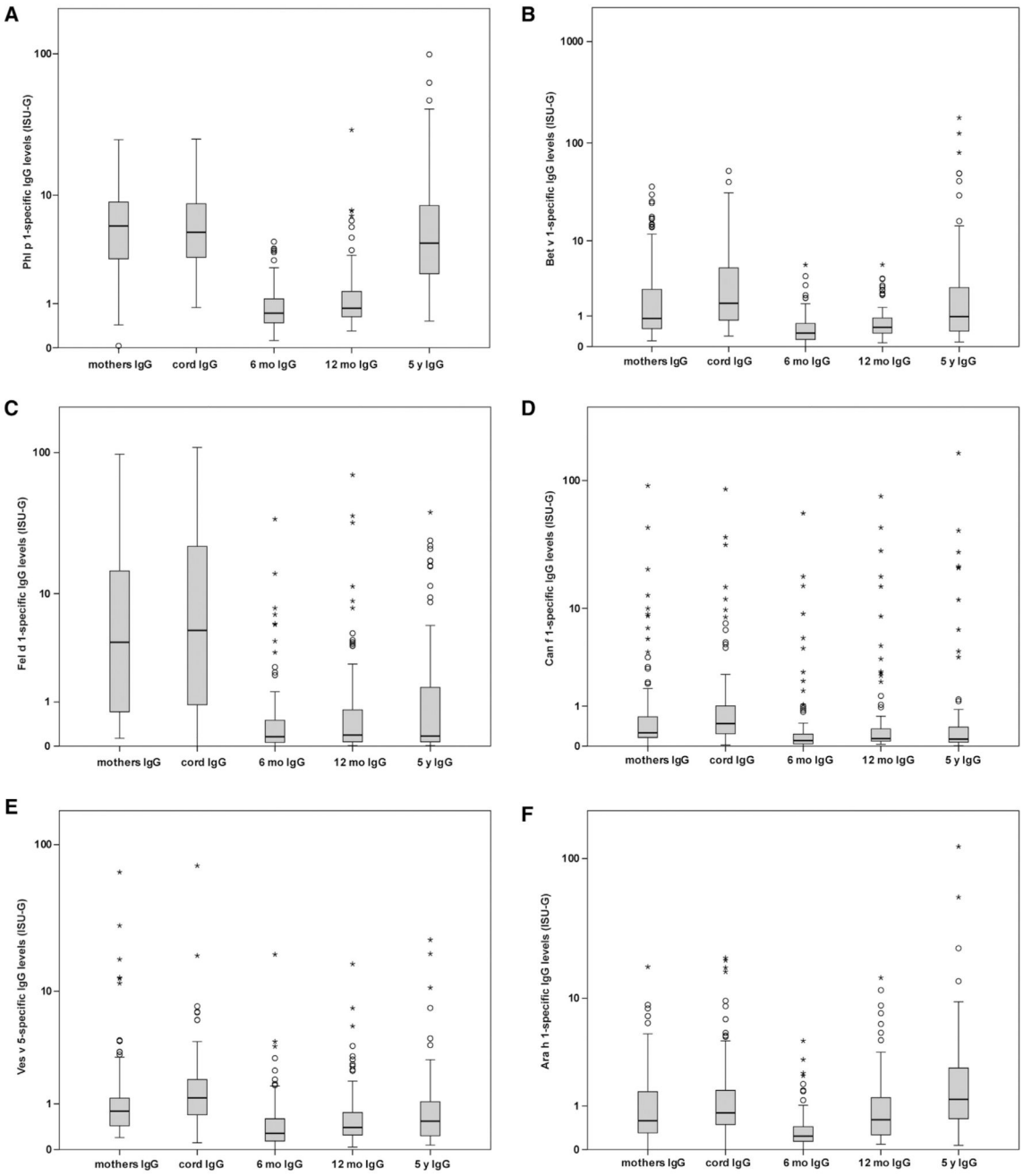

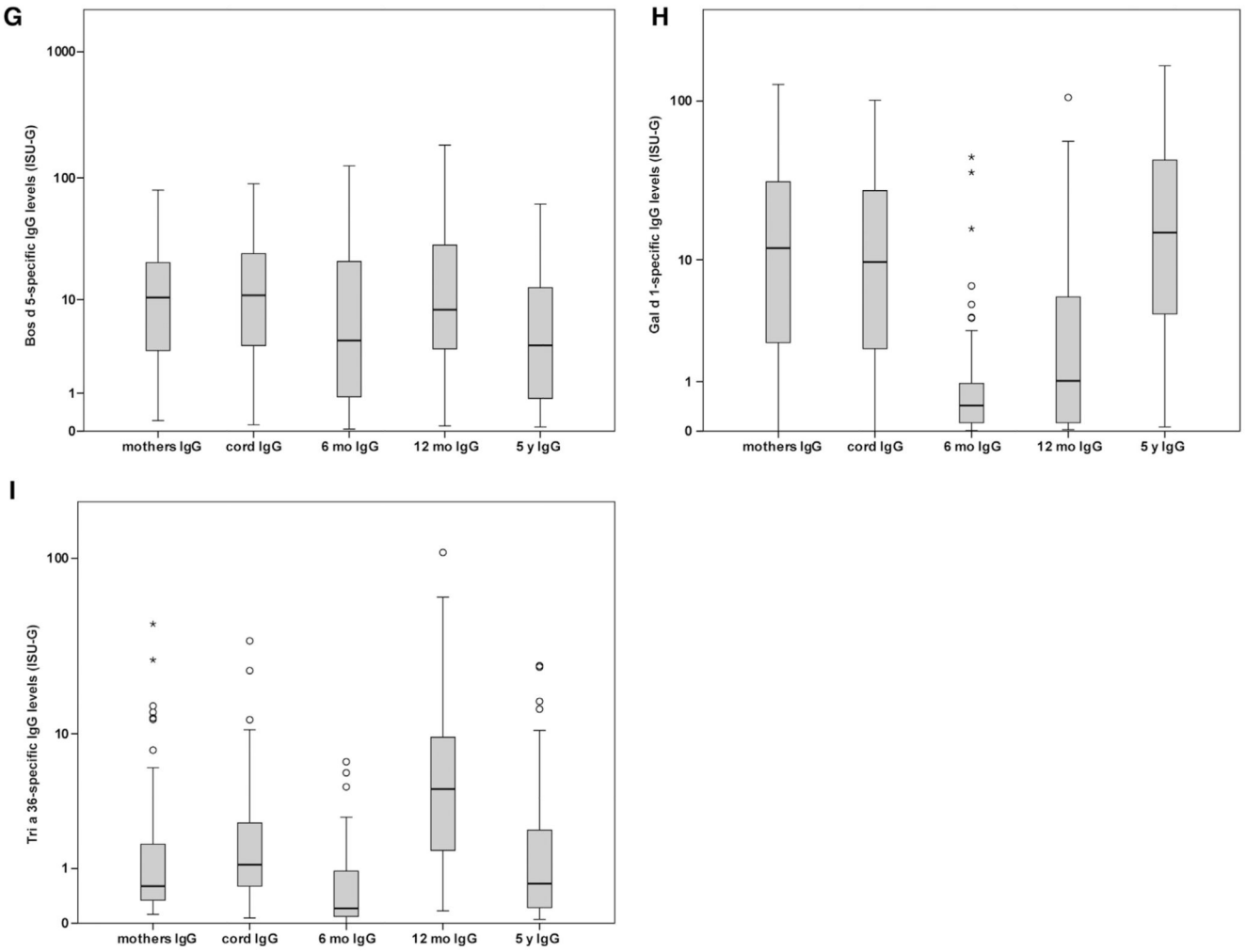

Fig 4.

Allergen-specific IgG levels measured in 99 families (mothers' plasma, cord blood, and children's blood at 6 months, 12 months, and 5 years) for frequently recognized respiratory allergens (**A**, Phl p 1; **B**, Bet v 1; **C**, Fel d 1; **D**, Can f 1), a frequent venom allergen (**E**, Ves v 5), and food allergens (**F**, Ara h 1; **G**, Bos d 5; **H**, Gal d 1; and **I**, Tri a 36) are shown. *x-axes*, Samples; *y-axes*, IgG levels as ISU-G. *Box plots* display first quartiles, medians, and third quartiles, and *whiskers* represent the range of data within 1.5 times the interquartile range); outliers (>1.5 times interquartile range) and extreme values (>3 times interquartile range) are represented by *open circles* and *asterisks*, respectively.

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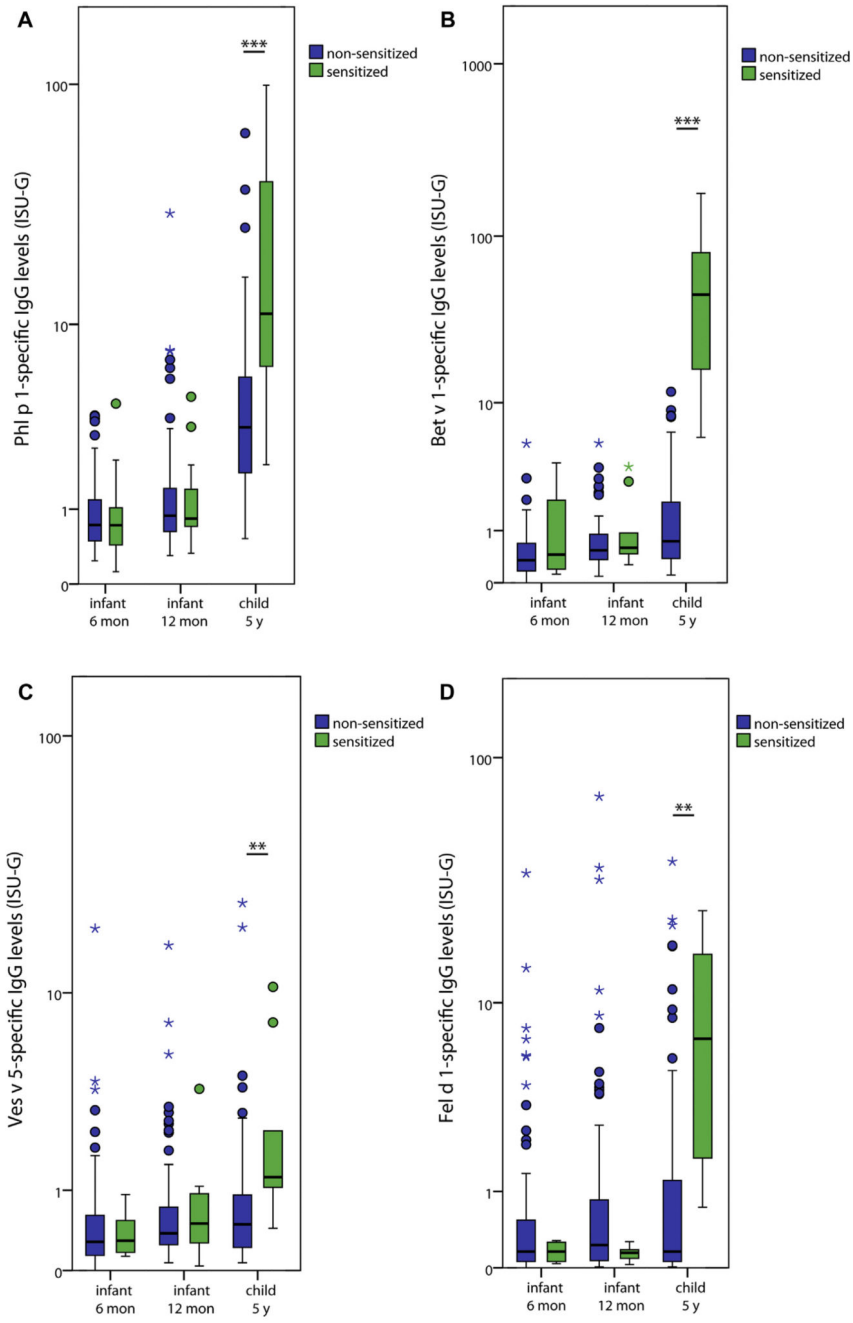

Fig 5.

IgG levels specific for the most frequently recognized allergens (*y-axes*, ISU-G) in samples from children at 6 months, 12 months, and 5 years of age *(x-axes)* grouped according to the presence (≥0.3 ISU, green) or absence (blue) of allergen-specific IgE sensitization in children at 5 years of age. **A**, Phl p 1 (nonsensitized children, n = 80; sensitized children, n = 19). **B**, Bet v 1 (nonsensitized, n = 89; sensitized, n = 10). **C**, Ves v 5 (nonsensitized, n = 89; sensitized, n = 10). **D**, Fel d 1 (nonsensitized, n = 93; sensitized, n = 6). *Box plots* display first quartiles, medians, and third quartiles, and *whiskers* represent range of data within 1.5

times the interquartile range; outliers (>1.5 times interquartile range) and extreme values (>3 times interquartile range) are represented by *open circles* and *asterisks*, respectively. *$P < .05$, **$P < .01$, and ***$P < .001$.

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Table I

Demographic data for the participating families, including allergy-related data

	Anthroposophic (n = 22)	Partly anthroposophic (n = 42)	Nonanthroposophic (n = 35)	*P* value*
Parents				
Mother's age (y)	32 (23-46)	31 (19-42)	31 (21-41)	.87
Father's age (y)	35 (20-48)	36 (21-58)	34 (24-42)	.52
Mother sensitized to aeroallergens†	6/22 (27%)	16/42 (38%)	7/35 (20%)	.22
Father sensitized to aeroallergens†	11/22 (50%)	16/40 (40%)	11/34 (32%)	.44
Father smoking	2/22 (9%)	11/41 (27%)	6/35 (17%)	.21
Mother during pregnancy				
Antibiotics	1/22 (4.5%)	6/41 (15%)	6/35 (17%)	.47
Vegetarian diet	7/22 (32%)	6/41 (15%)	0/30 (0%)	.002
Smoking	1/22 (4.5%)	2/41 (4.9%)	2/35 (5.7%)	1.00
Living on a farm with animals	2/21 (9.5%)	3/39 (7.7%)	3/34 (8.8%)	1.00
Delivery				
Home delivery	14/22 (63%)	11/42 (26%)	0/35 (0%)	<.001
Child				
Sex (female)	10/22 (46%)	23/42 (55%)	21/35 (60%)	.57
Birth weight (g)	3629 (2480-4650)	3681 (2930-4900)	3585 (2905-4590)	.69
Gestational age at birth (completed weeks)	40 (36-42)	40 (36-43)	39 (37-41)	.23
Breast-feeding at 2 mo				
Exclusively	22/22 (100%)	39/42 (93%)	29/35 (83%)	.09
Partly	0/22 (0%)	3/42 (7.1%)	6/35 (17%)	
Breast-feeding at 6 mo				
Exclusively	11/22 (50%)	10/42 (24%)	2/34 (5.9%)	
Partly	10/22 (46%)	27/42 (64%)	28/34 (82%)	.004
Not	1/22 (4.5%)	5/42 (12%)	4/34 (12%)	
Breast-feeding at 12 mo				
Exclusively	0/22 (0%)	1/41 (2%)	0/35 (0%)	
Partly	12/22 (55%)	17/41 (42%)	6/35 (17%)	.01
Not	10/22 (45%)	23/41 (56%)	29/35 (83%)	
Pets in household <2 mo of age	7/22 (32%)	19/42 (45%)	18/35 (51%)	.37
Other contact with animals <2 mo of age	7/22 (32%)	11/42 (26%)	15/35 (43%)	.31
Child sensitized at 5 y of age to:				
Food allergens‡	3/22 (14%)	6/42 (14%)	12/35 (34%)	.09
Aeroallergens†	4/22 (18%)	10/42 (24%)	9/35 (26%)	.87
Food allergen and/or aeroallergenst† ‡	6/22 (27%)	12/42 (29%)	15/35 (43%)	.34

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	Anthroposophic (n = 22)	Partly anthroposophic (n = 42)	Nonanthroposophic (n = 35)	*P* value*
Child's symptoms up to 5 y of age				
Asthma ever diagnosed by doctors	0/22 (0%)	5/42 (12%)	3/35 (8.6%)	.25
Eczema ever diagnosed by doctors	2/22 (9%)	3/40 (7.5%)	5/35 (14%)	.67
Allergic rhinitis ever diagnosed by doctors	0/22 (0%)	2/42 (4.8%)	0/35 (0%)	.51
Food allergy ever diagnosed by doctors	2/21 (9.5%)	3/40 (7.5%)	4/35 (11%)	.90

Categorical variables are indicated as numbers/total numbers (percentages). Continuous variables are presented as medians (minimums-maximums).

*P values: categorical variables, Fisher exact test; continuous variables, Kruskal-Wallis test.

†Classified as sensitized if IgE level was 0.35 kU_A/L or greater measured by using Phadiatop (mix of 11 inhalant allergens).

‡Classified as sensitized if IgE level was 0.35 kU_A/L or greater for at least 1 of the 6 food allergens analyzed by using the fx5 food mix (Thermo Fisher Scientific).

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Table II

Numbers and percentages of children (n = 99) with allergen-specific IgE reactivity to microarrayed allergens at 5 years of age, as well as numbers of maternal IgG levels of 30 ISU-G or greater

Allergen	No.	Percentage	No. of maternal IgG levels ≥30 ISU-G	Allergen	No.	Percentage	No. of maternal IgG levels ≥30 ISU-G
rPhl p 1	19	19.2	0	nFel d 2	2	2.0	0
nCyn d 1	15	15.2	1	nGal d 5	2	2.0	0
rBet v 1	10	10.1	2	nGly m 6	2	2.0	1
rVes v 5	10	10.1	1	rHev b 6.01	2	2.0	0
rPol d 5	9	9.1	0	rHev b 8	2	2.0	0
rCor a 1.0401	8	8.1	0	rMer a 1	2	2.0	0
rPru p 1	7	7.1	0	rPhl p 6	2	2.0	1
rAra h 8	6	6.1	0	rPru du 4	2	2.0	0
rFel d 1	6	6.1	15	rTri a Trx	2	2.0	0
rMal d 1	6	6.1	0	rTri a 12	2	2.0	1
nPhl p 4	5	5.1	1	rAna o 2	1	1.0	0
nCup a 1	4	4.0	1	rAna o 3	1	1.0	0
rDer f 2	4	4.0	0	rAra h 2	1	1.0	0
rDer p 2	4	4.0	0	nAra h 6	1	1.0	0
rEqu c 1	4	4.0	6	nArt v 1	1	1.0	0
rPhl p 5	4	4.0	0	rAsp f 6	1	1.0	0
nPla a 2	4	4.0	1	nCan f 3	1	1.0	0
rAln g 1	3	3.0	0	rCan f 5	1	1.0	5
rApi g 1	3	3.0	1	rDer p 4	1	1.0	0
rApi m 1	3	3.0	0	rDer p 5	1	1.0	1
nAra h 1	3	3.0	0	rDer p 15	1	1.0	1
rCan f 1	3	3.0	2	rDer p 37	1	1.0	0
nCry j 1	3	3.0	0	nEqu c 3	1	1.0	1
nDer f 1	3	3.0	0	rFel d 4	1	1.0	6
nGal d 1	3	3.0	30	nGal d 3	1	1.0	0
rHev b 5	3	3.0	1	nGly m 5	1	1.0	0
nJug r 2	3	3.0	0	rHev b 3	1	1.0	0
rPhl p 2	3	3.0	0	rJug r 1	1	1.0	0
rAni s 1	2	2.0	0	nMus m 1	1	1.0	1
rBet v 2	2	2.0	0	nPen m 2	1	1.0	0
rCan f 2	2	2.0	1	rPhl p 11	1	1.0	0
rCan f 6	2	2.0	2	rPhl p 12	1	1.0	0
nDer p 1	2	2.0	0	rPru p 3	1	1.0	6
rDer p 21	2	2.0	0	rTri a DH	1	1.0	1

Allergen	No.	Percentage	No. of maternal IgG levels ≥30 ISU-G	Allergen	No.	Percentage	No. of maternal IgG levels ≥30 ISU-G
rDer p 23	2	2.0	4	rCor a 1.01	1	1.0	0

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Table III

Correlations between allergen-specific IgG levels determined in plasma of mothers, cord blood, breast milk, and plasma from children obtained at different ages, as well as allergen-specific IgE levels in children at 5 years of age

	IgG						IgE
All allergens	**Mother**	**Cord blood**	**Breast milk**	**Infant, 6 mo**	**Infant, 12 mo**	**Child, 5 y**	**Child, 5 y**
IgG							
Mother	1						
Cord blood	0.826	1					
Breast milk	0.647	0.644	1				
Infant, 6 mo	0.522	0.540	0.529	1			
Infant, 12 mo	0.360	0.427	0.415	0.599	1		
Child, 5 y	0.431	0.432	0.507	0.512	0.602	1	
IgE							
Child, 5 y	0.165	0.197	0.21	0.222	0.247	0.312	1

Spearman correlation coefficients are listed for all tested allergens and for the data sets indicated.