

Effects of maternal diet during late pregnancy and lactation on the development of IgE and egg- and milk-specific IgE and IgG antibodies in infants

G. LILJA, A. DANNAEUS*, T. FOUCARD*, V. GRAFF-LONNEVIG, S. G. O., JOHANSSON† and H. ÖMAN†

Sachs' Children's Hospital, Karolinska Institute, Stockholm, *Paediatric Department of Akademiska Hospital, Uppsala, and †Department of Clinical Immunology, Karolinska Hospital, Stockholm, Sweden

Summary

The IgE levels and food-allergen-specific IgE- and IgG-antibodies (Ab) to ovalbumin (OA), ovomucoid (OVO) and β -lactoglobulin (BLG) were determined up to 18 months of age in 163 infants born to women who were atopic. A high (HIGH group) or a low (REDUCED group) intake of hen's egg and cow's milk by the mother during the third trimester gave no significant differences in the concentrations of IgE or in IgE-Ab (OVO, BLG) and IgG-Ab (OA, OVO, BLG). Similarly, a prolongation of the abstention diet to the early lactation period did not influence the immune response. The IgG-Ab levels to all three food allergens decreased significantly ($P < 0.001$) in both study groups between birth and 2 months of age, but then increased significantly ($P < 0.001$) between 6 and 18 months of age. The presence in serum of IgE-Ab to OVO (≥ 0.15 PRU/ml) was associated with significantly higher IgG-Ab levels to OVO at 6 months ($P < 0.001$) and at 18 months ($P < 0.05$). Infants with positive skin-prick tests (SPT) to OA and OVO showed higher IgG-Ab levels at 6 and 18 months of age than did infants with negative SPT reactions to the two egg allergens. This indicates a relation between the IgE- and IgG-Ab response and it also suggests that some individuals are 'high responders' to both types of immunoglobulin isotypes while others are 'low responders'.

Clinical and Experimental Allergy, Vol. 21, pp. 195–202. Submitted 20 February 1990; revised 4 September 1990; accepted 28 September 1990.

Introduction

The risk of developing food allergy symptoms is greater in early infancy than later in life. Allergic reactions, especially to cow's milk and hen's egg, have therefore been studied extensively during this period of life [1]. Food allergy and other types of atopy are related to increased concentrations of IgE and IgE antibody levels (IgE-Ab) to food allergens [1,2]. The interaction between genetic [3] and environmental factors [4] is responsible for the IgE sensitization. Exposure to food allergens *in utero* [5–7] or via breast milk [8] has been suggested as a way to induce the IgE response in the fetus/young infant and the subsequent development of atopic diseases during early infancy.

On the contrary, the passage of IgG antibodies (IgG-Ab) from the mother to the infant [1,9,10] has been considered to have an inhibitory effect on the IgE response during early infancy. A high IgG/IgE-Ab ratio [11] and high levels of IgG-Ab [12] in cord blood have been thought to influence the development of food allergy. However, significantly higher levels of IgG-Ab to milk proteins have been found in infants with adverse reactions to cow's milk than in non-allergic controls [13].

The purpose of this study was to evaluate the effect of a high or a low intake of potent food allergens by the mothers during late pregnancy and early lactation on the IgE concentrations, levels of IgE- and IgG-Ab to ovalbumin (OA), ovomucoid (OVO) and β -lactoglobulin (BLG) and the development of atopy in the infants up to 18 months of age. The effect on *in vivo* parameters has been reported earlier [14].

Correspondence: Dr G. Lilja, Sachs' Children's Hospital, Sachsgatan 1, S-118 95 Stockholm, Sweden.

Subjects and methods

One-hundred and sixty-two pregnant women with respiratory allergy were randomly allocated during late pregnancy to a diet with a low or a high ingestion of cow's milk and hen's egg, the REDUCED ($n=79$) and the HIGH groups ($n=83$), respectively [14]. In the REDUCED group 25 women continued with a low ingestion of hen's egg and cow's milk during the first 2 months of lactation (REDUCED-A group). The remaining 54 women in the REDUCED group (REDUCED-B group) and all women in the HIGH group 'normalized' their ingestion of the two nutrients after delivery.

A total of 166 infants, 104 boys and 62 girls, was born. There were 81 infants in the REDUCED and 85 in the HIGH group, including two pairs of twins in each group. Three infants in the HIGH group left the study during the first 6 months after delivery and thus 82 infants in this group remained to be evaluated at 18 months of age. The mothers of the infants in the REDUCED group had higher IgE levels ($P<0.01$) at the start of the study and a higher incidence of atopic dermatitis ($P<0.05$) than the women in the HIGH group [14]. Otherwise, confounding background parameters for the development of atopic disease, such as smoking habits of the parents and exposure to furred animals, did not differ between the two groups of infants [14; (χ^2 analysis)]. The feeding pattern and the time of introduction of solid foods were standardized [14].

Immunoglobulin determinations

The levels of IgE were determined by a sensitive PRIST method with a lower detection limit of 0.125 kU/l, as described previously [15]. IgE-Ab to OVO and BLG were analysed by RAST, and by prolonging the incubation time in the RAST test we were able to detect IgE-Ab levels down to a concentration of ≥ 0.15 PRU/ml [15]. The IgG-Ab levels were analysed by ELISA [15] and the results were expressed in arbitrary units (AU)/ml, with a lower detection limit of 1 AU/ml. The IgG-Ab levels below this limit were given the value of 1.0 AU/ml in the statistical analyses.

Assay variabilities between runs for the extra-sensitive PRIST assay were 13% and 8% for IgE levels of 0.2 and 0.9 kU/l, respectively. Within runs, the variability of the IgE assay was 2%. The interassay variations in the specific IgG assays for OA, OVO and BLG were 12% for all three tests. The intra-assay variations were 4%, 4% and 3%, respectively.

Serum samples were collected at delivery and at 2, 6 and 18 months of age and were stored at -20°C , pending analysis. All analyses were performed in duplicate. When the serum volume was insufficient for performing all the

Table 1. IgE levels (kU/l) in infants in the REDUCED ($n=81$) and the HIGH ($n=82$) groups

	REDUCED	HIGH	<i>P</i>
Delivery	0.33 (79) <0.125–1.2	0.24 (80) <0.125–0.70	n.s.
2 months	0.78 (78) 0.3–2.4	0.88 (78) 0.3–3.1	n.s.
6 months	4.83 (77) 1.3–17.5	4.84 (81) 1.1–20.8	n.s.
18 months	10.61 (79) 2.4–47.6	11.21 (81) 2.9–43.7	n.s.

Results are presented as the geometric mean and the geometric mean $\pm$ s.d.

The numbers of serum samples available for analysis in each group are given in brackets.

n.s., not significant.

tests, the priority order was total IgE, IgE-Ab to OVO, IgE-Ab to BLG and, finally, IgG-Ab to OA, OVO and BLG.

Skin-prick tests

The procedure for skin-prick tests (SPTs) with OA, OVO, BLG allergens and cow's milk (3% fat) has been described previously [14].

Statistical analyses

Chi-squared analyses, Fisher's exact test, Kruskal–Wallis one-way analysis by ranks, Mann–Whitney *U*-test, Wilcoxon's paired signed rank sum test and the Spearman rank correlation test were used to evaluate the results. A *P* value (two-tailed) ≤ 0.05 was considered significant.

Ethics

The study was approved by the Human Research Ethics Committee of Karolinska Institute, Stockholm. Informed consent was given by all the women before entering the study.

Results

IgE levels

In both groups the IgE levels steadily increased from birth to 18 months of age. No significant differences in the IgE concentrations were found between the REDUCED and

Table 2. Number of infants with IgE-Ab (≥ 0.15 PRU/ml) to OVO or BLG at 6 and 18 months after birth in relation to feeding pattern during the first 6 months of life

	Breast-feeding > 6 months		Breast-feeding > 2 < 6 months + soy formula		Breast-feeding > 2 < 6 months + soy formula/ cow's milk		Breast-feeding < 2 months + soy formula	
	R (n=43)	H (n=45)	R (n=16)	H (n=17)	R (n=8)	H (n=5)	R (n=14)	H (n=15)
6 months	3/38*	4/45†	1/14	2/17	0/7	0/5	0/13	1/13
18 months	9/42‡	4/42†	1/15	2/17†	0/8	0/5	0/14	2/15

R, REDUCED group; H, HIGH group.

* number of infants with a positive test/number of infants tested.

† One infant had a RAST ≥ 0.15 PRU/ml to both OVO and BLG.

‡ Two infants had a RAST ≥ 0.15 PRU/ml to both OVO and BLG.

the HIGH groups during the entire observation period (Mann-Whitney *U*-test; Table 1). Likewise there were no significant differences in IgE concentrations between the REDUCED-A and -B groups.

IgE antibody levels

IgE-Ab to OVO and BLG were not detected in cord blood. At 6 months of age three children in the REDUCED group and five in the HIGH group had IgE-Ab in serum to OVO (≥ 0.15 PRU/ml). One child in each study group had a value ≥ 0.35 PRU/ml, which corresponded to RAST class 1. At 18 months of age five children in the REDUCED and six in the HIGH group showed IgE-Ab to OVO, and seven of these were ≥ 0.35 PRU/ml. IgE-Ab to BLG were found in 15 infants—eight in the REDUCED and seven in the HIGH group—but only two (one in the REDUCED group at 6 months and one in the HIGH group at 18 months) were ≥ 0.35 PRU/ml. The numbers of infants with IgE-Ab to OVO and BLG did not differ significantly between the REDUCED and the HIGH groups (Fisher's exact test).

The presence of IgE-Ab to OVO and BLG was not influenced by the avoidance of hen's egg and cow's milk during early lactation (REDUCED-A group). Similarly, the number of infants with IgE-Ab to food allergens was not influenced by the duration of breast-feeding or the type of feeding pattern up to 6 months of age when comparing the REDUCED and HIGH groups and when studying the results within the HIGH group (Table 2; Fisher's exact test). However, in the REDUCED group at 18 months of age there were significantly ($P < 0.05$; Fisher's exact test) more infants with positive RAST (≥ 0.15 PRU/ml) to OVO and/or BLG among infants

who were strictly breast-fed for ≥ 6 months (9/42) than among infants breast-fed for < 6 months (1/37). In the first group eight of nine infants with a positive RAST belonged to the REDUCED-B group.

IgG antibody levels

Changes with age within groups. In both the REDUCED and HIGH groups there was a significant decrease in the levels of IgG-Ab to OA, OVO and BLG between delivery and 2 months of age (Wilcoxon; $P < 0.001$; Fig. 1). Between 2 and 6 months of age the IgG-Ab levels to OA remained unchanged in both groups. The levels of IgG-Ab to OVO decreased significantly in both the REDUCED ($P < 0.001$) and the HIGH groups ($P < 0.01$) while the levels of the IgG-Ab to BLG in the HIGH group increased ($P < 0.01$). However, between 6 and 18 months of age the IgG-Ab levels to all three food allergens increased significantly ($P < 0.001$) in both groups of infants.

Differences between the groups. Highly significant ($P < 0.001$) correlations in IgG-Ab levels to the three selected food allergens between cord blood and maternal blood samples were observed at delivery, although the IgG-Ab levels in both diet groups were higher in cord serum than in the corresponding maternal serum samples [15]. There were no significant differences between the infants in the REDUCED and HIGH groups in the levels of IgG-Ab to the three selected food allergens, either in cord blood or in blood samples collected at 2, 6 and 18 months of age (Mann-Whitney *U*-test, Fig. 1). Moreover, no significant group differences were found in the relative

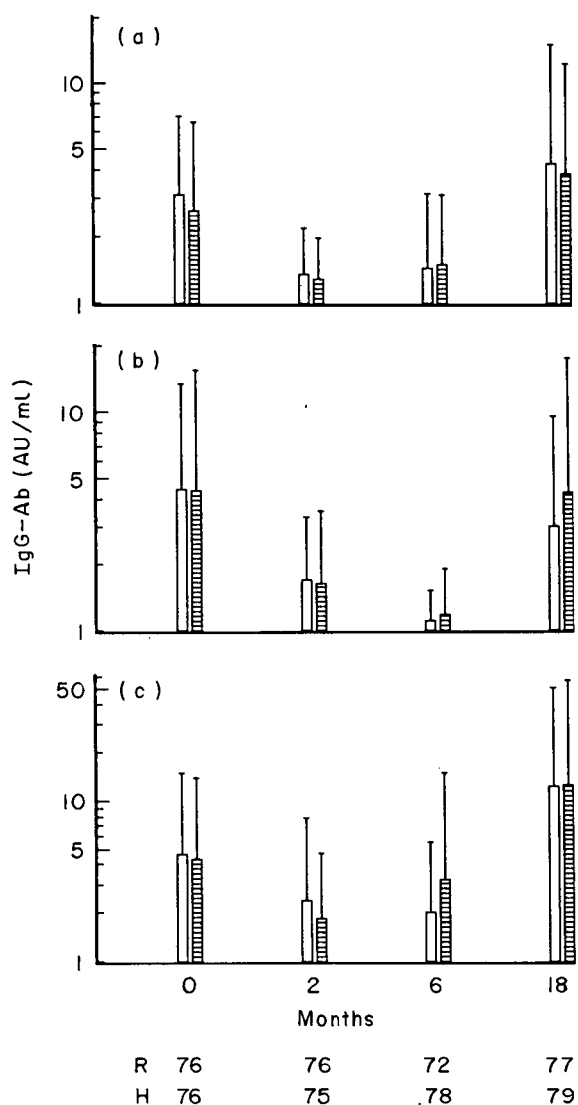


Fig. 1. IgG-Ab levels (AU/ml) to ovalbumin (a) ovomucoid (b) and β -lactoglobulin (c) in cord blood and at 2, 6 and 18 months of age in the REDUCED (R; □) and HIGH (H; ▨) groups. Geometric means + s.d. are presented. The figures below the graphs represent the number of available analyses. No significant group differences were observed on any sampling occasion.

changes (%) in IgG-Ab levels to OA, OVO and BLG between birth and 2 months, 2 and 6 months, and between 6 and 18 months of age. Furthermore, the levels of IgG-Ab were not influenced by a reduced intake of hen's egg and cow's milk during the first 2 months of lactation (REDUCED-A group).

Infant feeding. There were no significant differences in the IgG-Ab levels between infants in the REDUCED group and in the HIGH group in relation to different feeding

patterns during the first 6 months of life, except a weakly significant ($P < 0.05$) difference with higher IgG-Ab levels to OVO at 18 months of age among infants who were breast-fed > 2 but < 6 months and who received soy formula and belonged to the HIGH group (data not shown). Thus, the IgG-Ab results with respect to the feeding pattern in the two diet groups were combined for analysis (Table 3). At 6 months of age there was a significant ($P < 0.05$; Kruskal-Wallis) difference in IgG-Ab levels to OA in relation to different feeding patterns. A further analysis of this difference shows that infants who were strictly breast-fed during the first 6 months of age differed significantly ($P < 0.05$; Mann-Whitney *U*-test) from those infants who were breast-fed for shorter periods or who had received soy and/or milk-based formula. This difference in IgG-Ab levels to OA was even more pronounced ($P < 0.01$; Mann-Whitney *U*-test) when infants who were breast-fed for > 6 months ($n = 88$) were compared to infants who were breast-fed for < 6 months ($n = 75$). The IgG-Ab levels to OVO were not influenced by differences in feeding patterns. However, there was a significant ($P < 0.05$; Kruskal-Wallis) difference in IgG-Ab levels to BLG in relation to feeding patterns at 6 months of age (Table 3). Thus, infants who were on cow's milk-based formula at 6 months of age had higher ($P \leq 0.05$; Mann-Whitney *U*-test) IgG-Ab levels to BLG than did those who were fed breast-milk or soy formula.

Association with RAST and SPT. Since no significant differences in the skin-prick tests (SPTs) [14] and RAST results were observed between the infants in the REDUCED-A, REDUCED-B and HIGH groups, they were considered as one group with respect to IgG-Ab response. The IgG-Ab levels to OVO at 6 months were significantly (Mann-Whitney *U*-test; $P < 0.001$) higher among infants with IgE-Ab to OVO ≥ 0.15 PRU/ml ($n = 8$, geometric mean (Gm) = 1.67) than among infants with no detectable IgE-Ab to OVO ($n = 139$, Gm = 1.11). This difference ($P < 0.05$) still existed at 18 months (RAST-OVO ≥ 0.15 PRU/ml; $n = 11$, Gm = 8.28 ; and RAST-OVO < 0.15 PRU/ml; $n = 144$, Gm = 3.36). No significant differences in the IgG-Ab levels to BLG were found at 6 months between infants with or without the presence of IgE-Ab to BLG. At 18 months, however, there was a tendency ($P = 0.06$) towards higher concentrations of IgG-Ab to BLG in infants with IgE-Ab to BLG ≥ 0.15 PRU/ml ($n = 11$, Gm = 25.6) than in infants with no detectable IgE-Ab to BLG ($n = 143$, Gm = 11.6).

The association between the IgE- and IgG-Ab responses to food allergens was further evaluated by comparing the IgE-Ab levels in infants with negative and positive SPT results. Except for the IgG-Ab concentra-

Table 3. Levels (AU/ml) of IgG-Ab to OA, OVO and BLG in relation to type of feeding pattern

Months	Type of allergen	Breast-feeding > 6 months (n=88)	Breast-feeding > 2 < 6 months + soy formula (n=33)	Breast-feeding > 2 < 6 months + soy formula/ cow's milk (n=13)	Breast-feeding < 2 months + soy formula (n=29)	P*
2	OA	1.3	1.4	1.3	1.3	n.s.
	OVO	1.7	1.7	1.9	1.7	n.s.
	BLG	2.1	1.6	4.6	1.9	n.s.
6	OA	1.7	1.3	1.3	1.1	<0.05
	OVO	1.2	1.0	1.5	1.1	n.s.
	BLG	2.7	1.9	5.7	2.1	<0.05
18	OA	4.0	4.6	4.3	3.7	n.s.
	OVO	3.7	3.8	3.1	3.3	n.s.
	BLG	11.5	8.1	25.1	18.2	n.s.

Results in the REDUCED and HIGH groups are considered together.

Geometric means are given.

n.s., not significant.

* Kruskal-Wallis one-way analysis by ranks.

Table 4. Levels (AU/ml) of IgG-Ab to OA, OVO and BLG in relation to skin-prick test (SPT) results

	Pos.* SPT	Neg. SPT	P†
6 months			
OA	3.43 (20) 1.3-9.0	1.30 (131) <1.0-2.4	<0.001
OVO	1.45 (8) <1.0-3.0	1.12 (143) <1.0-1.7	<0.05
BLG	83.38 (2) —	2.45 (149) <1.0-8.5	<0.05
18 months			
OA	8.92 (21) 2.5-31.9	3.61 (135) 1.2-11.3	<0.01
OVO	9.82 (14) 2.4-40.7	3.25 (142) <1.0-11.2	<0.01
BLG	27.64 (4) 5.1-149.6	12.18 (152) 2.8-52.1	n.s.

The results in the REDUCED and HIGH groups are considered together.

Geometric mean and geometric mean $\pm$ s.d. are given.

Number of available analyses within parentheses.

* $\geq$ histamine weal (1 mg/ml).

† Mann-Whitney U-test.

tions to BLG at 18 months of age, significantly higher values were found among infants with positive than with negative SPTs to the offending food allergen (Table 4).

Discussion

Opinions differ as to whether the maternal intake of potent food allergens during pregnancy and the lactation period affects the IgE response in the offspring during early infancy [5-7,9,10,16]. In animal models [9,10], a suppression of IgE synthesis in the offspring has been found after immunization with egg protein during pregnancy. These results concerning the development of 'atopic tolerance' in rats were not applicable to the present study. Differences in the study design and genetic predisposition often make it difficult to compare results from animal models with the results of clinical studies in humans.

The present study shows that neither a high nor a low maternal intake of cow's milk or hen's egg towards the end of pregnancy or a normal or low intake during the breast-feeding period affects the IgE or IgE-Ab levels of the infants up to 18 months of age. The dietary manipulations did not affect the development of atopic symptoms or SPT reactivity [14]. Other recent studies support the thesis that dietary manipulations, even total elimination diets, during the pregnancy and lactation periods do not affect total IgE levels [17-19]. However, some conflicting

results were reported in a recent study [19], e.g. a trend ($P=0.06$) was noted towards a smaller number of infants with a positive RAST (≥ 0.35 PRU/ml) to milk or egg among children whose mothers avoided milk, egg and fish during lactation, as compared to those on a normal diet. In that study [19] both parents were atopic or else the infants had a cord blood IgE level ≥ 0.9 kU/l. This stronger atopic heredity may explain the observed effect of the diet on the RAST results. Another reason why we have not seen this difference may be the comparatively small number of subjects in our REDUCED-A group ($n=25$).

The observation in both study groups that IgE-Ab to egg proteins were present in serum and in the skin [14] before the introduction of the offending food in the infant's diet suggests that sensitization may occur independently of maternal diet during the perinatal period. This phenomenon has also been observed in previous studies [19,20]. The possibility of sensitization through breast-milk is well established [8], but other ways of inducing IgE sensitization may also prove effective. Sensitization *in utero* [5-7], by means of anti-idiotypic antibodies [21], or after birth by the inhalation route [22] are other possible mechanisms.

Breast-feeding has been thought to give protection against the development of atopy. Thus, the mothers in this study were encouraged to breast-feed for at least 6 months [14]. Nevertheless, IgE-Ab to the selected food allergens developed in both the REDUCED and HIGH groups, and mostly among infants who were strictly breast-fed for 6 months or more (Table 2). This is further evidence of a possible sensitization through breast milk. However, the association between prolonged breast-feeding and the presence of food-specific IgE-Ab was significant ($P<0.05$) only in the REDUCED group at 18 months of age. Moreover, out of the nine infants in the REDUCED group with a positive food allergen RAST at 18 months of age and a longer 'strictly breast-feeding period', eight (89%) belonged to the group of mothers who normalized their food intake after delivery (REDUCED-B). This does not support the hypothesis that a hypoallergenic ('low-dose') diet during lactation more easily initiates IgE sensitization [23].

IgG-Ab to food allergens have been thought to affect IgE-mediated reactions [9-12]. Since IgG-Ab are actively transferred from mother to fetus during intrauterine life [15,24] it has been hoped that a change in the maternal diet during pregnancy would also change the IgG-Ab concentrations in the newborns. However, our results, like other recently published data [15,17,24], show that the IgG-Ab levels of cow's milk and hen's egg in cord blood were not related to the mother's ingestion of the offending food during late pregnancy. Likewise, there was

no difference between the effect of an elimination diet during early lactation (REDUCED-A group) and a normalized intake (REDUCED-B and HIGH group) on the IgG-Ab levels. This finding was also reported in a recent study [19]. However, a restricted diet of cow's milk and hen's egg given to the mother in conjunction with breast-feeding of the infant has resulted in higher IgG-Ab levels to OA, but not to BLG, at 6 weeks of age [17]. Despite these variations in food-allergen-specific IgG-Ab levels during the first months of life, no currently available study shows any lasting difference in IgG-Ab levels reflecting differences in maternal diets during the perinatal period.

If IgG-Ab levels to food allergens are related to the development of atopy during early infancy it may be interesting to investigate the importance of dietary factors other than the maternal diet. Early life is a period characterized by a poorly developed secretory immune system and this provides one explanation of an increased mucosal permeability and subsequent immune response to ingested antigens. It may also explain why infants in this study who were fed cow's milk during early infancy showed higher levels of IgG-Ab to BLG than did breast-fed infants and it underlines the major importance of the infant's own food intake for the immunoglobulin response [17,25,26]. Increasing levels of IgA- and IgM- but not of IgG-Ab to BLG have also been found in strictly breast-fed infants during the first months of life [25]. In this study breast-feeding was associated with significantly higher IgG-Ab levels of OA, but not to OVO, at 6 months of age. These observations suggest that different food allergens induce different immunoglobulin responses both systemically (IgG) and locally in the intestine (IgA, IgM) [25,27].

The increased levels of IgG-Ab to OVO in infants with positive RAST to OVO that we observed are in agreement with previous reports [2,19]. In contrast to hen's egg proteins there seems to be a less pronounced association between IgE- and IgG-Ab to cow's milk allergens [2,19,28] which further emphasizes that different food allergens have different immunogenicities regarding different classes of immunoglobulin. The observed parallelism between the IgG- and IgE-Ab responses to food allergens has also been observed previously for inhalant allergens during childhood [28] and in adults with atopic dermatitis with or without inhalant allergy [29]. However, in a comparison of atopic dermatitis patients with a healthy control group, higher levels of food-allergen-specific IgG-Ab (OVO, BLG) were found, but the IgG-Ab levels did not correlate to SPT or RAST results [30]. Although IgG- and IgE-Ab responses to food allergens may be influenced by differences in feeding patterns, the tendency of these immunoglobulin isotypes to undergo

parallel changes may be governed by genetic factors [28]. However, for diagnostic purposes in atopy the determinations of IgG-Ab levels to food allergens have only a limited value.

Acknowledgments

The statistical analyses were carried out by Per Näsman, University of Stockholm. This study was supported by the following organizations: the Swedish Medical Research Council (grant no. 16X-105), the National Association for Prevention of Asthma and Allergy (RmA), the Karolinska Institute and Konsul Th Berghs Foundations. Soya-Semp was kindly supplied by Semper AB, Stockholm, Sweden.

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