Early diet and the risk of allergy: what can we learn from the prospective birth cohort studies GINIplus and LISAplus?[1–5]

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ABSTRACT

Recently, the American Academy of Pediatrics and the European Society of Pediatric Gastroenterology, Hepatology, and Nutrition published new guidelines on early nutrition and allergy prevention in infants and children. This article reviews epidemiologic evidence from 2 prospective German birth cohort studies, the GINIplus and the LISAplus, regarding maternal diet during pregnancy and feeding patterns in early life and the risk of allergy in light of the new recommendations. The 2 cohorts include a total of 9088 infants who were recruited within different regions of Germany between 1995 and 1999. A subgroup of 2252 infants with a hereditary risk of atopy was enrolled in a double-blind, randomized trial to investigate the effect of feeding regimen in infancy on the development of allergy with the strict recommendation that allergenic solid food be introduced late in the study. The results of the GINIplus and LISAplus studies mainly support the new finding regarding allergy prevention that a delayed introduction of solid foods or the avoidance of highly allergenic foods during the first year does not seem to be beneficial for allergy prevention. A very early introduction of solid foods and a high diversity before week 17 of age may increase the risk of later allergy. We showed that a high intake of margarine, vegetable oils, and some allergenic fruit and vegetables during pregnancy was associated with an increased risk of allergies, especially eczema. Because maternal diet during pregnancy is not reflected in the current recommendations, it should be the focus of future studies. *Am J Clin Nutr* 2011;94(suppl):2012S–7S.

INTRODUCTION

Recently, the American Academy of Pediatrics (1) and the European Society of Pediatric Gastroenterology, Hepatology and Nutrition (2) published new guidelines on early nutrition and allergy prevention in infants and children. They recommend exclusive or full breastfeeding for about 6 mo as a desirable goal. Complementary feeding should not be introduced in any infant before 17 wk; all infants should start complementary feeding by 26 wk (2). No recommendations to avoid or delay the introduction of potentially allergenic foods, such as fish or eggs, were made. Furthermore, no recommendations on maternal diet during pregnancy or lactation were made.

In the 2 prospective German birth cohort studies GINIplus (German Infant Nutritional Intervention plus environmental and genetic influences) and LISAplus (Influences of Lifestyle-Related Factors on the Immune System and the Development of Allergies in Childhood plus the influence of traffic emissions and genetics), the effects of maternal diet during pregnancy and complementary feeding on allergic diseases later in childhood have been investigated. The aim of the present article, therefore, was to review the results of the LISAplus and GINIplus studies in light of the new recommendations for allergy prevention.

SUBJECTS AND METHODS

Description of the 2 birth cohorts

The present article is based on 2 ongoing German birth cohorts, the GINIplus and the LISAplus studies. The GINIplus study is an ongoing birth cohort initiated to prospectively investigate the influence of nutrition intervention during infancy plus air pollution and genetics on allergy development. Between September 1995 and July 1998, a total of 5991 term newborn infants were recruited from 2 regions of Germany (Munich, Bavaria, and Wesel, North-Rhine-Westfalia). Detailed descriptions of the screening and recruitment process for the GINIplus study have been published previously (3, 4). Briefly, the cohort is composed of an intervention group (n = 2252) and a nonintervention group (n = 3739). The intervention group included high-risk infants, defined as those with at least one parent or sibling with a history of allergic diseases. In this prospective, double-blind intervention trial, newborns were randomized at birth to one of 3 hydrolyzed formulas or to a conventional cow milk formula. Mothers were advised to breastfeed exclusively during the strict intervention period of 4 mo, and formulas were provided only if breastfeeding was not feasible or wanted. Furthermore, it was recommended that solid foods not be introduced during the first 4 mo of life and thereafter

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[4] Supported by the Commission of the European Community, within the FP 6 priority 5.4.3.1 Food quality and safety (Early nutrition programming-long term follow up of efficacy and safety trials and integrated epidemiological, genetic, animal, consumer and economic research, EARNEST, Food-CT-2005-007036).

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only one new food item be introduced per week. Potentially allergenic foods, such as cow milk and dairy products, eggs, fish, tomatoes, nuts, soy products, and citrus fruit, were to be avoided entirely during the first year. Parents filled in yearly self-administered questionnaires on health, nutrition, and living conditions, participated in structured interviews at the study centers, and kept weekly diaries on the children's nutrition and health for 24 wk.

The nonintervention group included infants with no family history of allergy and infants with a positive family history who did not take part in the intervention trial because of logistic reasons or because the parents had refused to participate. This group did not receive any of the intervention procedures and received the yearly questionnaires only.

The LISAplus study is an ongoing population-based birth cohort study of infants designed to assess "Influences of Lifestyle related Factors on the Immune System and the Development of Allergies in Childhood." The design and objective of this prospective birth cohort study have been described in detail elsewhere (5, 6). In brief, 3097 newborns were recruited between November 1997 and January 1999 from 4 German cities: Munich, Leipzig, Wesel, and Bad Honnef. Questionnaire data on family history of atopy, parental education, smoking during pregnancy, and maternal diet during the last 4 wk of pregnancy were obtained shortly after delivery. Self-completion questionnaires on the children's health and on lifestyle factors from birth to 2 y and at 4 y and 6 y were filled in biannually by the parents. Blood samples were obtained at 2 and 6 y.

The 2 studies share similar, but not identical, study protocols. For both studies, approval by the respective local ethics committees and written consent from participants' families were obtained.

Food-frequency questionnaire

Maternal food intake during the last 4 wk of pregnancy was assessed with use of a semiquantitative food-frequency questionnaire administered shortly after childbirth. For each food item, the mothers reported their average consumption frequency over the previous 4 wk according to 5 categories that ranged from "< 2 times/month or never" to "≥4 times/week." Each food-frequency variable was dichotomized at a cutoff close to the 66th percentile, or alternatively to the 33rd percentile, to categorize children into high or low intake in accordance with maternal food consumption frequencies. For more details readers should refer to the original article (6).

Complementary feeding

When the infants were 12 mo old, parents were asked about breastfeeding practices and about the timing of solid-food introduction into the child's diet. Possible answer choices included "1st until 4th month," "5th/6th month," "7th to 12th month," and "solid food item not yet introduced." Forty-eight single food items were classified into the following 8 solid-food groups: vegetables, cereal, fruit, meat, dairy products, egg, fish, and other (soybean, nuts, cacao, and chocolate). Summary exposure variables included *any solids,* defined by the timing of first introduction of any of the above-mentioned solid-food items, and *solid diversity*, defined at 4 mo and at 6 mo by the total number of different food groups that were included in the child's diet at that time.

Definition of outcomes

Doctor-diagnosed eczema was defined as parent report of a physician's diagnosis of eczema during the preceding 6 mo during the first 2 y of the LISAplus study, and during the preceding 12 mo after the second year in the LISAplus study, and during the whole study period in the GINIplus study. The question was "Did a physician diagnose any of the following diseases . . . allergic or atopic eczema/dermatitis?" Lifetime prevalence of eczema was assumed if eczema had been diagnosed at any time point.

Symptomatic eczema was defined as parent report of an itching eczema within the preceding 6 mo (in the semiannual questionnaires during the first 2 y) and 12 mo (in the biannual questionnaires from the second year onwards), that was either recurrent or lasted for more than 6 mo (in the first year) or 2 wk (from the second to the sixth year) and that affected the skin creases, face, neck, extremities, hands, feet, or trunk (not underneath the diaper).

Allergic sensitization against food allergens was defined as a specific serum immunoglobulin E (IgE) concentration ≥0.35 kU/L against pediatric food allergens (egg, cow milk, wheat, peanut, soybean, and codfish). A positive result in this screening test was followed by measurement of the single allergens egg, cow milk, and peanut at 2 y.

Allergic sensitization against inhalant allergens was defined as a specific serum IgE concentration ≥0.35 kU/L against at least one of the following allergen mixes: house dust allergens (*Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, German cockroach, and house dust), cat dander, mixed molds (*Penicillium notatum*, *Cladosporium herbarum*, *Aspergillus fumigatus*, and *Alternaria alternata*), or seasonal allergens (timothy grass, mugwort, English plantain, ribwort, wall pellitory, and birch pollen).

Total and specific serum IgE concentrations were assayed with use of the CAP-RAST FEIA system (Pharmacia Diagnostics, Freiburg, Germany) in accordance with the manufacturer's instructions. The limit of detection for specific IgE was 0.35 kU/L, and values ≥0.35 kU/L were considered positive.

Statistical methods

Complementary feeding and allergies: LISAplus study

To investigate the associations between different solid-food measures with doctor diagnoses and symptoms of eczema, asthma, allergic rhinitis, and sensitization outcomes in the LISAplus study, multivariate logistic-regression analyses were performed, adjusted for study center, parental atopy, child's sex, parental education, birth weight (only at 6 y), and breastfeeding type. For any solids, those children whose first introduction of any solid within the first 4 mo were taken as the reference group. For solid diversity, those children who had had no introduction of solids within the first 4 mo were taken as the reference group. Multivariate analyses were performed in parallel for the whole cohort and for the stratum of children without early skin or allergic symptoms, with these effects considered to be undistorted by reverse causality.

Complementary feeding and allergies: GINIplus study

Multiple repeated-measures models were performed to investigate the association between different solid-food measures

and eczema outcomes in the GINIplus study. To model longitudinal data with missing outcome because of loss to follow-up, generalized estimation equations were used, and results were presented as adjusted odds ratio (aOR) with 95% CIs. All models were controlled for the fixed set of risk and confounding factors, family history of allergic eczema, and type of milk feeding. The factors sex, study area, siblings, parental education, maternal smoking before pregnancy, exposure to passive smoking, and birth weight were considered but were not included in the models because no confounding effects were seen.

Maternal diet during pregnancy: LISAplus study

To estimate the association between maternal food intake during pregnancy and eczema and allergic sensitization in the offspring in the LISAplus study, multiple logistic regression analysis was applied. he adjusted model included study area (Munich, Leipzig, Wesel, and Bad Honnef), sex, maternal age at delivery ($\leq$31 or $>$31 y), maternal smoking during second or third trimester of pregnancy, level of parental education (very high, high, medium, or low), exclusive breastfeeding for $\geq$4 mo, parental history of atopic diseases (asthma, hay fever, or eczema; no parents atopic, one parent atopic, and both parents atopic), season of birth, and all dietary variables.

RESULTS

Complementary feeding

For detailed results, readers should refer to the original articles that presented data from the LISAplus (7, 8) and the GINIplus (9) studies. Here, the results are reviewed in accordance with the outcomes analyzed.

Timing of solid-food introduction

Doctor-diagnosed allergic diseases

There was no evidence that indicated a protective effect of a delayed introduction of solid foods beyond the fourth to the sixth or beyond the sixth month of life, up to the age of 6 y, on doctor-diagnosed eczema, allergic rhinitis, or asthma (**Figure 1**). However, there was a borderline statistically significant trend for decreasing eczema risk at the age of 6 y with a delay of solid-food introduction beyond the end of the fourth month in children without early skin or allergic symptoms.

Symptoms of allergic diseases

No statistically significant associations were observed between the timing of solid-food introduction and allergic symptoms (**Figure 2**). However, there was a trend that a later introduction of solid-food groups beyond the fourth month of age decreases the odds of symptomatic eczema in children without early skin or allergic symptoms at the ages of 2 y and 6 y. There was, however, no additional protective effect when the introduction of solids was postponed to later than 6 mo.

Solid-food diversity

Doctor-diagnosed allergic diseases

No relation between the diversity of solid foods at the age of 4 mo (**Figure 3**) and 6 mo (data not shown) and doctor-diagnosed eczema during the first 4 y of life emerged. At the age of 6 y, the association between eczema and a high diversity of solid foods (3–8 food groups) at the age of 4 mo was statistically significant.

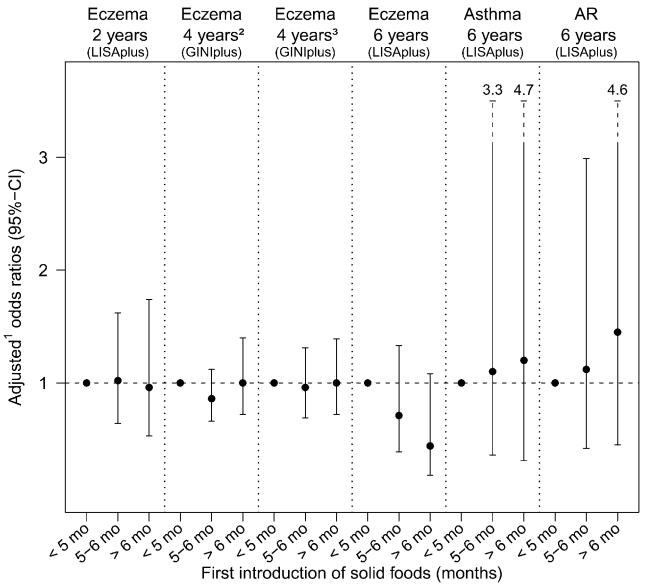

FIGURE 1. Association between timing of first introduction of solid foods and doctor diagnosis of allergic diseases up to the age of 6 y. Multiple logistic regression analyses were performed by using data from the LISAplus (Influences of Lifestyle-Related Factors on the Immune System and the Development of Allergies in Childhood plus the influence of traffic emissions and genetics) study for eczema at 2 and 6 y, as well as for allergic rhinitis (AR) and asthma at 6 y, and from the GINIplus (German Infant Nutritional Intervention plus environmental and genetic influences) study for eczema at 4 y. For the LISAplus study, children with early skin or allergic symptoms were excluded from the analyses. [1]Odds ratios adjusted for parental atopy and milk feeding type in the GINIplus study and for study center, parental atopy, sex, parental education, and breastfeeding type in the LISAplus study. [2]Data from the noninterventional subgroup of GINIplus. [3]Data from the interventional subgroup of GINIplus.

Symptoms of allergic diseases

Symptomatic eczema in children aged 2 y was positively associated with a high diversity of the diet at 4 mo in children without early skin or allergic symptoms (**Figure 4**). No effect was observed for eczema at later age or allergic rhinitis or asthma at the age of 6 y.

Maternal diet and eczema and allergic sensitization in the offspring: LISAplus study

High maternal intake of margarine (aOR: 1.49; 95% CI: 1.08, 2.04) and vegetable oils (aOR: 1.48; 95% CI: 1.14, 1.91) during pregnancy was positively associated, and high maternal fish intake (aOR: 0.75; 95% CI: 0.57, 0.98) was inversely associated, with doctor-diagnosed eczema during the first 2 y in the offspring. High celery (aOR: 1.85; 95% CI: 1.18, 2.89) and citrus fruit (aOR: 1.73; 95% CI: 1.18, 2.53) intake increased the risk of sensitization to food allergens. In turn, sensitization to inhalant allergens was positively related to a high maternal intake of deep-fried (hardened) vegetable fat (aOR: 1.61; 95% CI: 1.02, 2.54), raw peppers (aOR: 2.16; 95% CI: 1.20, 3.90), and citrus fruit (aOR: 1.72; 95% CI: 1.02, 2.92).

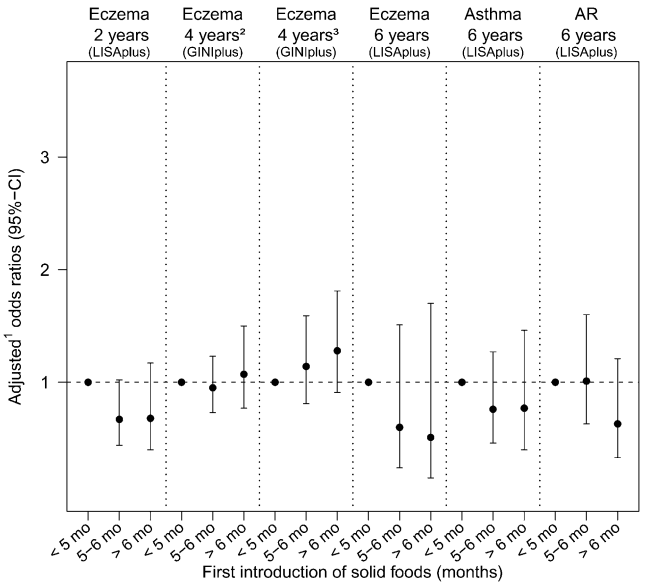

FIGURE 2. Association between timing of first introduction of solid foods and symptoms of allergic diseases up to the age of 6 y. Multiple logistic regression analyses were performed by using data from the LISAplus (Lifestyle-Related Factors on the Immune System and the Development of Allergies in Childhood plus the influence of traffic emissions and genetics) study for eczema at 2 and 6 y as well as for allergic rhinitis (AR) and asthma at 6 y and from the GINIplus (German Infant Nutritional Intervention plus environmental and genetic influences) study for eczema at 4 y. For the LISAplus study, children with early skin or allergic symptoms were excluded from the analyses. [1]Odds ratios adjusted for parental atopy and milk feeding type in the GINIplus study and for study center, parental atopy, sex, parental education, and breastfeeding type in the LISAplus study. [2]Data from the noninterventional subgroup of GINIplus. [3]Data from the interventional subgroup of GINIplus.

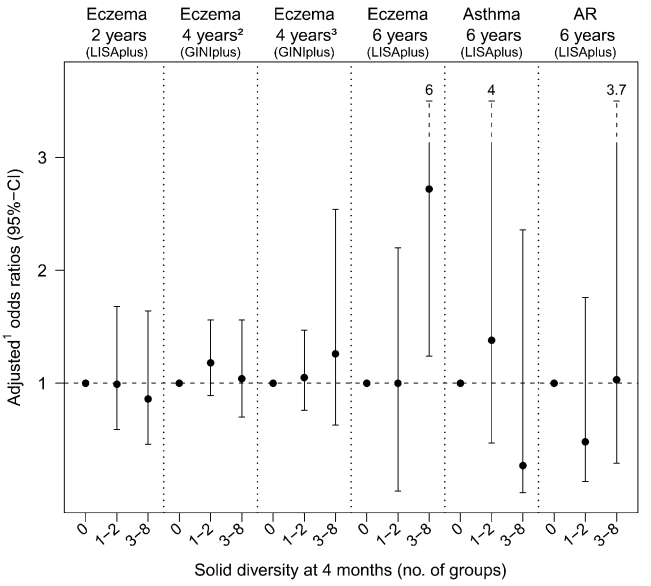

FIGURE 3. Association between solid-food diversity at 4 mo and doctor diagnosis of allergic diseases up to the age of 6 y. Multiple logistic regression analyses were performed by using data from the LISAplus (Lifestyle-Related Factors on the Immune System and the Development of Allergies in Childhood plus the influence of traffic emissions and genetics) study for eczema at 2 and 6 y as well as for allergic rhinitis (AR) and asthma at 6 y and from the GINIplus (German Infant Nutritional Intervention plus environmental and genetic influences) study for eczema at 4 y. For the LISAplus study, children with early skin or allergic symptoms were excluded from the analyses. [1]Odds ratios adjusted for parental atopy and milk feeding type in the GINIplus study and for study center, parental atopy, sex, parental education, and breastfeeding type in the LISAplus study. [2]Data from the noninterventional subgroup of GINIplus. [3]Data from the interventional subgroup of GINIplus.

No statistically significant associations were observed for either milk, yogurt, cheese, cream, eggs, butter, seeds, deep-fried (hardened) vegetable fat, nuts, raw carrots, spinach, cabbage, raw tomatoes, salad, vegetable juice, apples, kiwi, pineapple, bananas, strawberries, and fruit juice and any of the allergic outcomes.

DISCUSSION

The findings on early diet and the risk of allergic diseases reported from the birth cohort studies GINIplus and LISAplus show that an early introduction of solid foods with a high diversity of different solids, before the end of the fourth month, may increase the risk of later allergy, particularly eczema. However, a delayed introduction of solid foods beyond the sixth month of age or the avoidance of allergenic foods during the first year does not seem to be beneficial in allergy prevention. These findings are reflected in the new recommendation for allergy prevention recently published by the American Academy of Pediatrics (1) and the European Society of Pediatric Gastroenterology, Hepatology and Nutrition (2). Whereas the 2 societies do not support any dietary restriction during pregnancy, we showed that a high intake of margarine, vegetable oils, and some allergenic fruit and vegetables during pregnancy was associated with an increased risk of allergies, especially eczema.

Complementary feeding

Timing of solid-food introduction

The consensus guidelines recommend that complementary feeding should not be introduced before 17 wk and not later than 26 wk. The results of the LISAplus (7, 8) and GINIplus (9) studies largely support these guidelines. Clearly, there was no beneficial effect on eczema, allergic rhinitis, or asthma later in childhood when solid foods were introduced after the end of the sixth month. However, the effect on eczema of the introduction of solids past the fourth month was less clear, and a protective effect cannot be excluded.

The different results of the GINIplus and LISAplus studies may have been due to the differences in study design. Because early symptoms of eczema were not assessed in the GINIplus study, it could not be determined whether symptoms occurred before or after the introduction of solid foods, and thus reverse causation could not be controlled for. Therefore, because the potential effect of reverse causation could only be addressed within the LISAplus study, these findings may be more valid than those of the GINIplus study. Because of the low prevalence rates of doctor-diagnosed allergic rhinitis (4.1%) and asthma (2.1%) at age 6 y in our population-based cohort LISAplus, a lack of statistical power to detect significant associations may be why we did not observe any association for these outcomes.

Solid-food diversity

The consensus guidelines concluded that there is no convincing evidence that avoidance or delayed introduction of potentially allergenic foods decreases allergies. Our findings indicate that feeding a high diversity (3–8 groups) of solids to infants within the first 4 mo of life seems to increase the risk of eczema in children without early skin or allergic symptoms (LISAplus

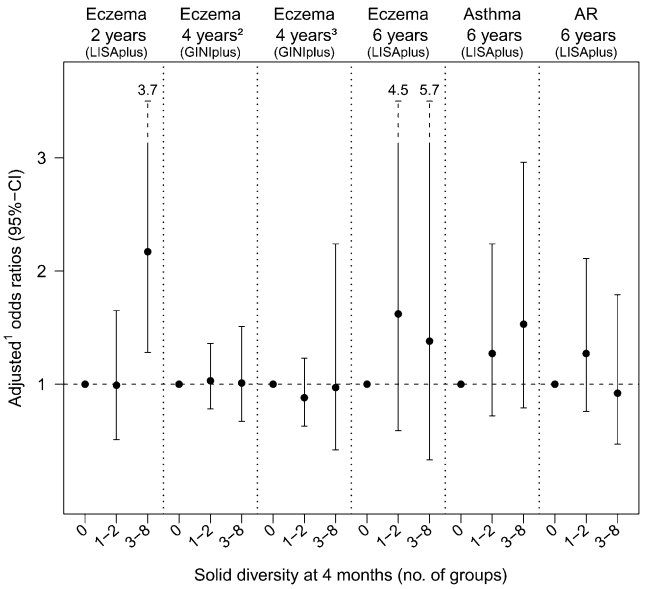

FIGURE 4. Association between solid-food diversity at 4 mo and symptoms of allergic diseases up to the age of 6 y. Multiple logistic regression analyses were performed by using data from the LISAplus (Lifestyle-Related Factors on the Immune System and the Development of Allergies in Childhood plus the influence of traffic emissions and genetics) study for eczema at 2 and 6 y as well as for allergic rhinitis (AR) and asthma at 6 y and from the GINIplus (German Infant Nutritional Intervention plus environmental and genetic influences) study for eczema at 4 y. For the LISAplus study, children with early skin or allergic symptoms were excluded from the analyses. [1]Odds ratios adjusted for parental atopy and milk feeding type in the GINIplus study and for study center, parental atopy, sex, parental education, and breastfeeding type in the LISAplus study. [2]Data from the noninterventional subgroup of GINIplus. [3]Data from the interventional subgroup of GINIplus.

study), although these results were not consistent across the different outcome measures and time points. Particularly, the effect was absent when eczema was modeled as lifetime prevalence up to the age of 4 y in the GINIplus cohort. However, as mentioned above, the results of the GINIplus study have to be interpreted with more caution.

Maternal diet during pregnancy

The new guidelines do not include recommendations for any dietary restriction during pregnancy. In the LISAplus study, however, margarine and vegetable oil intake during pregnancy was a risk factor for doctor-diagnosed eczema in the offspring, which has been ascribed to the high content of proinflammatory n−6 polyunsaturated fatty acids contained in margarine and vegetable oils (6). The intake of the potentially allergenic foods celery, citrus fruit, and raw sweet pepper was reported to increase the risk of allergic sensitization. Furthermore, a protective effect on eczema of maternal fish intake during pregnancy was reported. In Germany, for example, maternal fish intake during pregnancy has been recently recommended as a potential means to prevent allergic diseases (10).

The authors of this article argued that, because of multiple testing, significant associations might have occurred by chance. However, because the observed significant effects correspond with the biological mechanism of an association between the intake of foods rich in polyunsaturated fatty acids and antioxidants, or allergenic foods, they concluded that it is not likely that the results may be explained by chance alone. Therefore, maternal diet during pregnancy should be investigated further and considered when future guidelines for allergy prevention are formulated.

CONCLUSIONS

The findings of the LISAplus and GINIplus studies mainly support the new recommendations for allergy prevention. The intake of margarine, vegetable oils, citrus fruit, raw sweet pepper, and celery during pregnancy seemed to increase the risk of allergic outcomes, especially eczema. This finding should be investigated further.

The authors' responsibilities were as follows—SS: data summary and manuscript draft; and JH and SK: data interpretation and assistance with writing of manuscript. The sponsors were not influential in the study design, data collection, analysis, interpretation of results, or writing of the manuscript. None of the authors had a conflict of interest.

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APPENDIX A

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