Maternal diet during pregnancy in relation to eczema and allergic sensitization in the offspring at 2 y of age[1–3]

Stefanie Sausenthaler, Sibylle Koletzko, Beate Schaaf, Irina Lehmann, Michael Borte, Olf Herbarth, Andrea von Berg, H-Erich Wichmann, and Joachim Heinrich for the LISA Study Group

ABSTRACT

Background: Maternal diet during pregnancy might be one of the factors that influences fetal immune responses associated with childhood allergy.

Objective: We analyzed the association between maternal diet during the last 4 wk of pregnancy and allergic sensitization and eczema in the offspring at 2 y of age.

Design: Data from 2641 children at 2 y of age were analyzed within a German prospective birth cohort study (LISA). Maternal diet during the last 4 wk of pregnancy was assessed with a semiquantitative food-frequency questionnaire, which was administered shortly after childbirth.

Results: High maternal intake of margarine [adjusted odds ratio (aOR): 1.49; 95% CI: 1.08, 2.04] and vegetable oils (aOR: 1.48; 95% CI: 1.14, 1.91) during the last 4 wk of pregnancy was positively associated and high maternal fish intake (aOR: 0.75; 95% CI: 0.57, 0.98) was inversely associated with 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) intakes increased the risk of sensitization against food allergens. In turn, sensitization against inhalant allergens was positively related to a high maternal intake of deep-frying vegetable fat (aOR: 1.61; 95% CI: 1.02, 2.54), raw sweet pepper (aOR: 2.16; 95% CI: 1.20, 3.90), and citrus fruit (aOR: 1.72; 95% CI: 1.02, 2.92).

Conclusions: We suggest that the intake of allergenic foods and foods rich in n−6 polyunsaturated fatty acids during pregnancy may increase and foods rich in n−3 polyunsaturated fatty acids may decrease the risk of allergic diseases in the offspring. *Am J Clin Nutr* 2007;85:530–7.

KEY WORDS Maternal diet, pregnancy, allergic diseases, children

INTRODUCTION

Because prenatal life is a critical period for the development of the immune system, the role of intrauterine exposure in the etiology of allergic diseases has gained interest (1). In this context, maternal diet during pregnancy has been proposed to influence fetal immune responses that might predispose to childhood allergy (2).

During gestation, essential nutrients are transferred from the maternal to the fetal circulation across the placenta (3). Therefore, it might be possible that dietary factors associated with allergic diseases already exert their influence in utero. Complex transport mechanisms have been identified for antioxidants (4) and long-chain polyunsaturated fatty acids (5). Furthermore, it has been suggested that food and inhalant allergens ingested or inhaled by the mother cross the placental barrier (6).

Whether maternally derived allergens or immunogenic nutrients lead to an early specific sensitization in the fetus or induce allergen-specific tolerance is controversial (2, 7). Postnatally, a high dietary intake of n−6 polyunsaturated fatty acids (PUFAs) has been shown to be associated with an increased risk of allergic diseases because of their proinflammatory properties, whereas n−3 PUFAs and dietary antioxidants are supposed to have a protective effect on asthma and allergies (8).

Although there is a biological basis for a prenatal effect of dietary factors on the development of allergic diseases, the number of studies investigating this subject is very limited. The aim of the present study was to analyze prospectively in a large cohort whether maternal diet during the last 4 wk of pregnancy is associated with allergic sensitization or eczema in the offspring at 2 y of age.

SUBJECTS AND METHODS

Subjects

We analyzed data from the LISA (Influences of **L**ifestyle-related Factors on the **I**mmune **S**ystem and the Development of

[1] From the GSF–National Research Center for Environment and Health, Institute of Epidemiology, Neuherberg, Germany (SS, HEW, and JH); Dr von Hauner Children's Hospital (SK) and the Institute of Medical Data Management, Biometrics and Epidemiology (HEW), Ludwig-Maximilians–University of Munich, Munich, Germany; the Department of Pediatrics, Marien-Hospital Wesel, Wesel, Germany (BS and AvB); the Department of Environmental Immunology, UFZ–Center for Environmental Research, Leipzig, Germany (IL); the Departments of Pediatrics (MB) and Faculty of Medicine, Environmental Hygiene and Environmental Medicine (OH), University of Leipzig, Leipzig, Germany; the Municipal Hospital "St Georg" Leipzig, Children's Hospital, Leipzig, Germany (MB); and the Department of Human Exposure Research and Epidemiology, UFZ–Center for Environmental Research, Leipzig, Germany (OH).

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[3] Address reprint requests to J Heinrich, GSF–Institute of Epidemiology, Ingolstaedter Landstrasse 1, 85764 Neuherberg, Germany. E-mail: joachim.heinrich@gsf.de.

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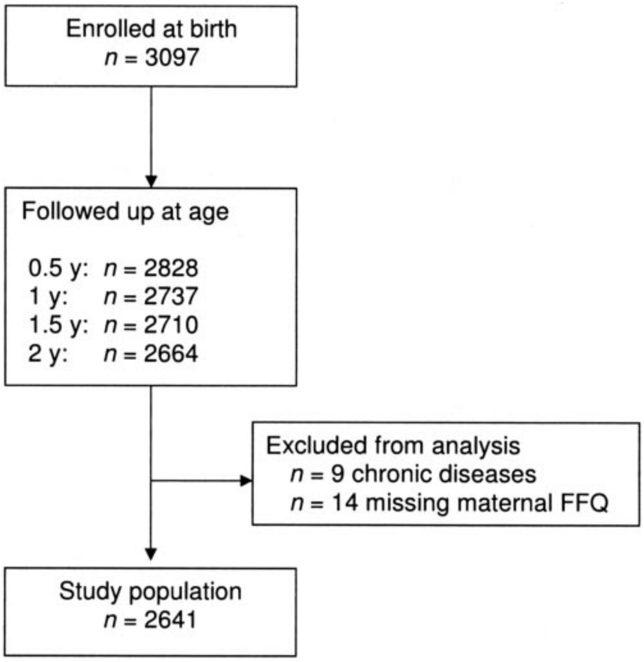

FIGURE 1. Flow chart showing the number of participants throughout the study. FFQ, food-frequency questionnaire.

Allergies in Childhood) Study. The design and objective of this prospective birth cohort study were described in detail elsewhere (9). In brief, 3097 newborns were initially 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 (median: 3 d). We collected data on the children's health and on lifestyle factors by using repeated parental-completed questionnaires at regular time intervals during the first 2 y of life (ie, at 6, 12, 18, and 24 mo of age). At 2 y of age, blood samples were drawn for total and specific immunoglobulin E (IgE) analysis.

For the present analysis, we selected subjects who had participated in the follow-up at 2 y, excluding children with chronic diseases (eg, celiac disease and metabolic disorders; $n = 9$) and children for whom no information on their mothers' diet during the last 4 wk of pregnancy was available ($n = 14$). Thus, the final study population consisted of 2641 children. The number of participants in each follow up period and the procedure used to select the final study population are shown in **Figure 1**. The local ethics committees approved the study protocol, and informed consent was obtained from the parents.

Dietary assessment

We assessed maternal food intake during the last 4 wk of pregnancy by using a semiquantitative food-frequency questionnaire (FFQ) administered shortly after childbirth. For each food item, the mothers reported their average consumption frequency over the past 4 wk according to 5 categories ranging from "< 2 times/mo or never" to "≥4 times/wk." Quantitative information was gathered on milk and yogurt intake only according to the following 4 categories: "never," "sometimes," "up to 0.5 L/d," and ">0.5 L/d" for milk intake and "never," "sometimes," "up to 200 g/d," and ">200 g/d" for yogurt intake. The original wording of the 26 food items selected for the present analysis is shown in **Appendix A**.

To estimate the effect of high compared with low maternal food intake during pregnancy on allergic outcomes, the children were categorized into 2 groups according to maternal food consumption frequency. Therefore, each food-frequency variable was dichotomized at a cutoff close to the 66th percentile. In this way, we contrasted the upper tertile (tertile 3) with the combination of the lowest and the middle tertiles (tertile 1 + tertile 2) for most of the food variables (cheese, cream, margarine, vegetable oils, seeds, deep-frying vegetable fat, nuts, fish, cabbage, celery, raw tomatoes, salad, vegetable juice, citrus fruit, apples, and strawberries). For some foods, considerably >33% of all subjects were in the highest consumption category; therefore, this procedure was not feasible. The cutoff was set at the 33rd percentile, and the combined middle and upper tertiles (tertile 2 + tertile 3) was contrasted with the lowest tertile (tertile 1) (milk, yogurt, eggs, butter, raw carrots, spinach, raw sweet pepper, exotic fruit, pineapple, bananas, and fruit juice). Thus, we used different reference categories for the logistic regression models.

Depending on the intake distribution of each food item, high maternal intake referred to different consumption frequencies. The high intake category included subjects who consumed foods ≥"2–3 times/mo" (deep-frying vegetable fat, spinach, celery, raw sweet pepper, and vegetable juice), "1–2 times/wk" (eggs, seeds, nuts, fish, raw carrots, cabbage, and strawberries), "3–4 times/wk" (cream, butter, vegetable oils, raw tomatoes, salad, citrus fruit, exotic fruit, and fruit juice), "≥4 times/wk" (cheese, margarine, apples, and bananas), or more than "sometimes" (milk and yogurt). A similar categorization strategy was recently described (10).

Outcome definition

Doctor-diagnosed eczema was based on a positive answer to the question, "Has a doctor diagnosed your child with allergic or atopic eczema in the past 6 mo? " Lifetime prevalence of doctor-diagnosed eczema was assumed if eczema has ever been diagnosed during the first 2 y of life.

Total and specific serum immunoglobulin E (IgE) concentrations were assayed by using the CAP-RAST FEIA system (Pharmacia Diagnostics, Freiburg, Germany) according to 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. Allergic sensitization against food allergens was defined as a specific serum IgE concentration ≥0.35 kU/L against pediatric food allergens (fx5) (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. 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 (hx2) (*Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, German cockroach, and house dust), cat dander (e1), mixed molds (mx1) (*Penicillium notatum*, *Cladosporium herbarum*, *Aspergillus fumigatus*, and *Alternaria alternata*), or seasonal allergens (rx1) (timothy grass, mugwort, English plantain, ribwort, wall pellitory, and birch pollen).

Statistical methods

Differences in the prevalence of eczema and allergic sensitization between the 2 categories of maternal food intake were tested by chi-square test. We further applied multiple logistic regression analysis to estimate the association between maternal food intake during the last 4 wk of pregnancy and eczema and allergic sensitization in their offspring. Odds ratios (ORs) and the corresponding 95% CIs were computed. First, we examined the crude association of maternal food intake with eczema and allergic sensitization. Then, we calculated an adjusted model that included study area (Munich, Leipzig, Wesel, and Bad Honnef), sex, maternal age at delivery (≤31 or >31 y), maternal smoking during second or third trimester of pregnancy, level of parental education (very high, high, medium, and low), exclusive breastfeeding for ≥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. Calculation of the variance inflation factor (11) did not indicate strong collinearity between dietary variables in the multiple logistic regression models.

We also tested for interactions between maternal food intake and maternal history of atopic diseases and duration of exclusive breastfeeding. All computations were performed by using the statistical analysis package SAS for WINDOWS (version 8.2; SAS Institute, Cary, NC). Two-sided P values <0.05 were considered statistically significant for all analyses.

RESULTS

The frequency of basic characteristics and possible confounding factors in our study population is shown in **Table 1**. Subjects were excluded when their mothers had completed the FFQ on maternal diet during pregnancy but did not return the 2-y questionnaire (n = 427). Compared with those, children of respondent mothers more likely lived in Munich (50.0% compared with 31.9%; P < 0.001) and were born to older mothers (31.3 y compared with 28.9 y; P < 0.001). They were less likely to have a smoking mother during pregnancy (10.1% compared with 24.2%; P < 0.001) and ≥2 older siblings (9.8% compared with 13.4%; P = 0.033), but were more likely to have parents with a very high level of education (54.6% compared with 31.8%; P < 0.001), at least one parent with atopic disease (52.7% compared with 43.0%; P < 0.001), and to have been breastfed for ≥4 mo (57.6% compared with 43.5%; P < 0.001). No statistically significant differences were observed between the responders and the excluded children with respect to sex (P = 0.375), birth weight (P = 0.713), or season of birth (P = 0.174).

The prevalences of eczema and allergic sensitization in the study population are shown in **Table 2**. At 2 y of age, 17.7% of all children had had doctor-diagnosed eczema, 9.3% were sensitized against food allergens, and 4.8% were sensitized against inhalant allergens. Of those sensitized against food allergens, milk (5.1%) and egg sensitization (5.4%) was most common. Sensitization to inhalant allergens was mainly ascribed to house dust allergens (2.8%).

Maternal diet during the last 4 wk of pregnancy turned out to be related to study area, maternal age at delivery, maternal smoking during pregnancy, level of parental education, and duration of exclusive breastfeeding. Only some foods, such as milk, cream, eggs, spinach, cabbage, vegetable juice, bananas, and strawberries, seemed to be largely independent of these factors.

The prevalences of eczema and allergic sensitization according to the intake categories for each food are shown in **Table 3**. Children of mothers with a high intake of margarine, vegetable oils, and seeds during pregnancy had a statistically significant higher lifetime prevalence of doctor-diagnosed eczema at 2 y of age than did children whose mothers had a low intake of these foods. Allergic sensitization against food allergens was more prevalent in children whose mothers had a high intake of celery and citrus fruit during pregnancy, whereas children sensitized against inhalant allergens were more frequently born to mothers with a high intake of raw sweet peppers.

In the logistic regression analysis, the results did not differ substantially between the crude and adjusted models. After adjustment for all potential confounders and dietary variables, the positive association between high maternal seed intake during the last 4 wk of pregnancy and eczema observed in the crude model attenuated to nonsignificance, whereas high fish intake showed a statistically significant protective effect on eczema for the first time. All other ORs became stronger, but the significance

TABLE 1
Basic characteristics of the LISA study population

Characteristic	Frequency
	n (%)
Study area	
Munich	1320 of 2641 (50.0)
Leipzig	785 of 2641 (29.7)
Wesel	269 of 2641 (10.2)
Bad Honnef	267 of 2641 (10.1)
Sex	
Male	1360 of 2641 (52.0)
Female	1281 of 2641 (48.0)
Maternal age at delivery	
≤31 y	1371 of 2639 (52.0)
>31 y	1268 of 2639 (48.0)
Maternal smoking during pregnancy[1]	
No	2272 of 2528 (89.9)
Yes	256 of 2528 (10.1)
Level of parental education	
Very high	1430 of 2617 (54.6)
High	536 of 2617 (20.5)
Medium	522 of 2617 (20.0)
Low	129 of 2617 (4.9)
Exclusively breastfed for ≥4 mo	
Yes	1506 of 2616 (57.6)
No	1110 of 2616 (42.4)
Parental history of atopic diseases[2]	
None	1248 of 2636 (47.3)
One parent atopic	1030 of 2636 (39.1)
Both parents atopic	358 of 2636 (13.6)
Number of older siblings	
0	1486 of 2641 (56.3)
1	895 of 2641 (33.9)
≥2	260 of 2641 (9.8)
Birth weight	
2500–3250 g	871 of 2641 (33.0)
3251–3650 g	897 of 2641 (34.0)
3651–5190 g	873 of 2641 (33.0)
Season of birth	
Spring (March-May)	572 of 2641 (21.7)
Summer (June-August)	722 of 2641 (27.3)
Fall (September-November)	696 of 2641 (26.4)
Winter (December-February)	651 of 2641 (24.6)

[1] During the second, third, or both trimesters.
[2] Asthma, hay fever, or eczema.

TABLE 2
Prevalence of eczema and allergic sensitization in the LISA study population at 2 y of age

Variable	Frequency
	n (%)
Doctor-diagnosed eczema[1]	446 of 2518 (17.7)
Allergic sensitization[2] against	
Any (food or inhalant) allergen	264 of 2139 (12.3)
Food allergens	200 of 2146 (9.3)
Cow milk	110 of 2144 (5.1)
Egg	116 of 2144 (5.4)
Peanut	37 of 2143 (1.7)
Any inhalant allergen	103 of 2138 (4.8)
House dust allergens	59 of 2143 (2.8)
Cat dander	26 of 2138 (1.2)
Mixed molds	9 of 2139 (0.4)
Seasonal allergens	32 of 2140 (1.5)

[1] Lifetime prevalence.
[2] Immunoglobulin E ≥ 0.35 kU/L.

level did not change. The results of the adjusted model are presented in **Table 4**. A high maternal intake of margarine and vegetable oils during pregnancy was positively associated with doctor-diagnosed eczema in their offspring, and a high maternal fish intake had a protective effect. The risk of allergic sensitization against food allergens in children increased when the maternal intake of celery and citrus fruit was high. In turn, sensitization against inhalant allergens was positively related to a high maternal intake of deep-frying vegetable fat, raw sweet peppers, and citrus fruit.

We further analyzed the relation between maternal intake of dairy products during pregnancy and sensitization against cow milk allergen in the offspring (data not shown). Children of mothers with a high cream intake had an increased risk of cow milk sensitization at 2 y of age (aOR: 1.62; 95% CI: 1.07, 2.45). No association between maternal egg intake during pregnancy and sensitization against egg allergen in the offspring could be observed.

Formal testing for interaction between maternal diet during pregnancy and maternal history of atopic diseases and time of exclusive breastfeeding was not statistically significant (data not shown).

DISCUSSION

The results of this prospective study suggest that maternal diet during the last 4 wk of pregnancy has an effect on the development of allergic diseases in the offspring. In particular, high maternal intakes of margarine, vegetable oils, deep-frying vegetable fat, celery, citrus fruit, and raw sweet peppers were positively associated with either eczema or allergic sensitization in children at 2 y of age. In turn, high fish consumption during the last 4 wk of pregnancy seemed to decrease the risk of eczema in childhood.

These findings are consistent with the hypothesis that the development of allergic diseases in childhood can be affected by intrauterine exposure to maternally derived allergens or proinflammatory factors modulating fetal immune responses (7). Margarine and vegetable oils with a high content of n−6 PUFAs might be responsible for the observed positive association between maternal intake of these fats and eczema in their offspring (12). This assumption is supported by the results of several studies reporting that margarine intake has an adverse effect on allergic diseases in children and adults (13–16). In contrast, there is evidence for a protective effect of fish intake on asthma and other allergic diseases (17–19), possibly because of the antiinflammatory properties of n−3 PUFAs contained in oily fish. An association between celery, citrus fruit, or raw sweet pepper intake and allergic sensitization has not yet been described in the literature. Because potential allergens in celery (20), citrus fruit—in particular oranges (21, 22)—and bell peppers (23) have been characterized, the observed associations might be linked to the allergenicity of these foods. However, the high antioxidant content of these foods should also be considered, although it seems unlikely that they play a causal role. We further cannot completely rule out that the findings either occurred by chance or are confounded by lifestyle factors, which were not assessed in this study. Therefore, prospective interventional trials are necessary to confirm these new observations.

Only a small number of studies have investigated the effect of maternal diet during pregnancy on the development of allergic diseases in the offspring. The role of early dietary modification on immune responses in children at high risk of atopy has been studied in a randomized placebo-controlled clinical trial including 83 atopic pregnant women. Subjects in the intervention group received fish-oil capsules containing n−3 PUFAs from 20 wk gestation. Neonates whose mothers took fish-oil supplements during pregnancy had significantly lower interleukin 13 concentrations in their cord blood than did the control group (24). Follow-up of the study further showed that infants in the intervention group were less likely to be sensitized to egg allergen and had significantly less severe atopic dermatitis at 1 y of age (25). In a nested case-control study including 691 schoolchildren, maternal fish consumption during pregnancy was assessed by retrospective telephone interviews. Oily a fish intake of at least monthly during pregnancy was significantly associated with a reduced asthma risk in childhood, but only in children born to asthmatic mothers (26). Although the recall of diet over a long period may be inaccurate, these results agree with our observation that a high maternal fish intake during pregnancy reduces the risk of atopic diseases in childhood.

Studies of the effects of maternal dietary allergen avoidance during pregnancy on atopic diseases and sensitization in the children provide conflicting findings (27–31). Although experimental interventions were mainly due to the dietary exclusion of cow milk, eggs, and peanuts, no study aimed to assess a potential reduction in atopic disease through the elimination of celery, citrus fruit, or raw sweet pepper intakes.

Martindale et al (32) prospectively investigated whether maternal antioxidant intake during pregnancy is related to respiratory symptoms and atopic diseases in early childhood. They reported a negative association between maternal vitamin E intake during pregnancy and wheeze in children at 2 y of age. Children, whose mothers were atopic also had a reduced risk of eczema. However, vitamin C intake was positively associated with wheeze and eczema. Unfortunately, we were not able to analyze our data with respect to antioxidant intake because of the limited number of food items included in our FFQ. However, there was no indication that the consumption of foods rich in antioxidants protects against allergic diseases.

TABLE 3
Prevalence of eczema and allergic sensitization in the children at 2 y of age according to intake categories of maternal food intake during pregnancy

Variable and intake category	Doctor-diagnosed eczema	P^1	Allergic sensitization against: Any allergens	P^1	Food allergens	P^1	Inhalant allergens	P^1
	n (%)		*n (%)*		*n (%)*		*n (%)*	
Milk								
Low	142 of 803 (17.7)		92 of 689 (13.4)		70 of 691 (10.1)		36 of 688 (5.2)	
High	304 of 1710 (17.8)	0.954	171 of 1445 (11.8)	0.318	129 of 1450 (8.9)	0.358	67 of 1445 (4.6)	0.548
Yogurt								
Low	197 of 1146 (17.2)		132 of 981 (13.5)		96 of 986 (9.7)		55 of 981 (5.6)	
High	249 of 1370 (18.2)	0.519	132 of 1154 (11.4)	0.158	104 of 1156 (9.0)	0.558	48 of 1153 (4.2)	0.121
Cheese								
Low	271 of 1551 (17.5)		166 of 1312 (12.7)		126 of 1315 (9.6)		66 of 1311 (5.0)	
High	174 of 964 (18.0)	0.712	98 of 824 (11.9)	0.604	74 of 828 (8.9)	0.618	37 of 824 (4.5)	0.568
Cream								
Low	322 of 1786 (18.0)		177 of 1507 (11.7)		132 of 1511 (8.7)		69 of 1506 (4.6)	
High	122 of 701 (17.4)	0.714	83 of 605 (13.7)	0.212	66 of 608 (10.9)	0.130	32 of 605 (5.3)	0.491
Eggs								
Low	127 of 670 (19.0)		71 of 563 (12.6)		51 of 566 (9.0)		30 of 563 (5.3)	
High	318 of 1838 (17.3)	0.337	192 of 1568 (12.2)	0.821	148 of 1572 (9.4)	0.777	73 of 1567 (4.7)	0.525
Butter								
Low	162 of 857 (18.9)		96 of 753 (12.7)		73 of 756 (9.7)		40 of 752 (5.3)	
High	274 of 1616 (17.0)	0.227	163 of 1350 (12.1)	0.652	122 of 1354 (9.0)	0.623	63 of 1350 (4.7)	0.507
Margarine								
Low	267 of 1626 (16.4)		171 of 1378 (12.4)		131 of 1382 (9.5)		66 of 1377 (4.8)	
High	163 of 801 (20.3)	0.017	82 of 691 (11.9)	0.722	62 of 694 (8.9)	0.687	32 of 691 (4.6)	0.870
Vegetable oils								
Low	281 of 1703 (16.5)		182 of 1465 (12.4)		138 of 1470 (9.4)		71 of 1464 (4.9)	
High	160 of 789 (20.3)	0.022	80 of 653 (12.3)	0.912	60 of 655 (9.2)	0.868	32 of 653 (4.8)	0.960
Seeds								
Low	311 of 1854 (16.8)		203 of 1578 (12.9)		155 of 1585 (9.8)		77 of 1578 (4.9)	
High	130 of 622 (20.9)	0.020	58 of 525 (11.0)	0.274	43 of 525 (8.2)	0.279	24 of 524 (4.6)	0.781
Deep-frying vegetable fat								
Low	281 of 1605 (17.5)		161 of 1353 (11.9)		127 of 1357 (9.4)		56 of 1352 (4.1)	
High	157 of 860 (18.3)	0.643	98 of 739 (13.3)	0.366	69 of 742 (9.3)	0.964	45 of 739 (6.1)	0.047
Nuts								
Low	351 of 1944 (18.1)		209 of 1668 (12.5)		157 of 1673 (9.4)		81 of 1668 (4.9)	
High	92 of 548 (16.8)	0.527	51 of 447 (11.5)	0.571	41 of 449 (9.1)	0.927	20 of 446 (4.5)	0.804
Fish								
Low	322 of 1727 (18.6)		177 of 1458 (12.1)		133 of 1464 (9.1)		70 of 1457 (4.8)	
High	122 of 771 (15.8)	0.088	85 of 663 (12.8)	0.659	66 of 664 (9.9)	0.530	32 of 663 (4.8)	0.982
Raw carrots								
Low	120 of 727 (16.5)		83 of 615 (13.5)		60 of 618 (9.7)		31 of 615 (5.0)	
High	323 of 1773 (18.2)	0.309	180 of 1511 (11.9)	0.315	140 of 1515 (9.2)	0.737	71 of 1510 (4.7)	0.741
Spinach								
Low	172 of 1027 (16.7)		107 of 861 (12.4)		85 of 867 (9.8)		39 of 860 (4.5)	
High	270 of 1464 (18.4)	0.276	156 of 1252 (12.5)	0.982	115 of 1253 (9.2)	0.628	63 of 1252 (5.0)	0.601
Cabbage								
Low	268 of 1548 (17.3)		164 of 1295 (12.7)		126 of 1300 (9.7)		60 of 1295 (4.6)	
High	178 of 955 (18.6)	0.400	100 of 832 (12.0)	0.660	74 of 834 (8.9)	0.526	43 of 831 (5.2)	0.571
Celery								
Low	367 of 2047 (17.9)		209 of 1739 (12.0)		154 of 1746 (8.8)		82 of 1738 (4.7)	
High	68 of 398 (17.1)	0.687	52 of 340 (15.3)	0.100	43 of 340 (12.6)	0.027	21 of 340 (6.2)	0.257
Raw tomatoes								
Low	310 of 1726 (18.0)		189 of 1476 (12.8)		147 of 1482 (9.9)		68 of 1475 (4.6)	
High	133 of 774 (17.2)	0.6381	75 of 647 (11.6)	0.436	53 of 648 (8.2)	0.205	35 of 647 (5.4)	0.430
Raw sweet pepper								
Low	133 of 744 (17.9)		65 of 637 (10.2)		55 of 642 (8.6)		18 of 637 (2.8)	
High	309 of 1750 (17.7)	0.896	196 of 1481 (13.2)	0.052	143 of 1483 (9.6)	0.434	83 of 1480 (5.6)	0.006
Salad								
Low	305 of 1707 (17.9)		181 of 1450 (12.5)		136 of 1457 (9.3)		72 of 1449 (5.0)	
High	139 of 797 (17.4)	0.794	82 of 677 (12.1)	0.809	64 of 677 (9.5)	0.930	30 of 677 (4.4)	0.589
Vegetable juice								
Low	345 of 1927 (17.9)		212 of 1622 (13.1)		158 of 1629 (9.7)		84 of 1621 (5.2)	
High	96 of 550 (17.5)	0.808	49 of 482 (10.2)	0.089	39 of 482 (8.1)	0.286	19 of 482 (3.9)	0.268
Citrus fruit								
Low	284 of 1570 (18.1)		150 of 1355 (11.1)		110 of 1359 (8.1)		64 of 1355 (4.7)	
High	157 of 909 (17.3)	0.608	109 of 757 (14.4)	0.025	86 of 759 (11.3)	0.014	38 of 756 (5.0)	0.755

(Continued)

TABLE 3 (*Continued*)

Variable and intake category	Doctor-diagnosed eczema	P[1]	Allergic sensitization against: Any allergens	P[1]	Food allergens	P[1]	Inhalant allergens	P[1]
Apples								
Low	296 of 1651 (17.9)		170 of 1397 (12.2)		127 of 1402 (9.1)		72 of 1396 (5.2)	
High	150 of 857 (17.5)	0.792	92 of 734 (12.5)	0.807	71 of 736 (9.6)	0.656	30 of 734 (4.1)	0.272
Exotic fruit								
Low	162 of 860 (18.8)		97 of 740 (13.1)		70 of 745 (9.4)		41 of 739 (5.5)	
High	282 of 1623 (17.4)	0.366	162 of 1373 (11.8)	0.381	126 of 1375 (9.2)	0.860	61 of 1373 (4.4)	0.259
Bananas								
Low	98 of 561 (17.5)		53 of 484 (11.0)		39 of 488 (8.0)		20 of 484 (4.1)	
High	346 of 1946 (17.8)	0.865	208 of 1643 (12.7)	0.314	159 of 1646 (9.7)	0.265	82 of 1642 (5.0)	0.436
Strawberries								
Low	295 of 1640 (18.0)		168 of 1412 (11.9)		132 of 1418 (9.3)		59 of 1411 (4.2)	
High	148 of 857 (17.3)	0.656	94 of 708 (13.3)	0.363	67 of 709 (9.4)	0.916	43 of 708 (6.1)	0.056
Fruit juice								
Low	120 of 722 (16.6)		73 of 621 (11.8)		54 of 625 (8.6)		33 of 624 (5.3)	
High	325 of 1782 (18.2)	0.338	190 of 1507 (12.6)	0.587	145 of 1510 (9.6)	0.486	70 of 1506 (4.6)	0.515

[1] Chi-square test.

Several possible limitations of the study need to be considered. Misclassification of dietary exposure is always a major issue in epidemiologic studies. We applied a semiquantitative FFQ, which provided qualitative information on maternal consumption frequencies during pregnancy, but no details on usual serving sizes were collected. However, a body of evidence supports the idea that the increment of additional quantitative information on diet is extremely small (33). This has been attributed to the fact that frequency explains most of the variation in total food intake and that intraindividual variability in serving sizes is generally greater than interindividual variability. Anyway, random misclassification of exposure would tend to bias effect estimates

TABLE 4

Logistic regression results for the association between maternal food intake during pregnancy and eczema and allergic sensitization in the offspring at the age of 2 y[1]

Variable	Doctor-diagnosed eczema	Allergic sensitization against: Any allergens	Food allergens	Inhalant allergens
Milk	1.04 (0.80, 1.34)	0.93 (0.67, 1.28)	0.95 (0.66, 1.37)	0.95 (0.58, 1.57)
Yogurt	0.99 (0.78, 1.27)	0.81 (0.59, 1.10)	0.89 (0.62, 1.27)	0.69 (0.43, 1.12)
Cheese	0.87 (0.68, 1.13)	0.99 (0.72, 1.36)	0.97 (0.68, 1.39)	0.93 (0.57, 1.53)
Cream	1.02 (0.78, 1.34)	1.20 (0.86, 1.67)	1.26 (0.87, 1.83)	1.26 (0.76, 2.08)
Eggs	0.81 (0.62, 1.06)	0.91 (0.56, 1.28)	0.93 (0.63, 1.38)	0.90 (0.53, 1.53)
Butter	1.08 (0.79, 1.46)	0.97 (0.66, 1.42)	0.93 (0.60, 1.43)	0.86 (0.48, 1.53)
Margarine	1.49 (1.08, 2.04)[2]	0.85 (0.56, 1.27)	0.80 (0.50, 1.27)	0.93 (0.50, 1.73)
Vegetable oils	1.48 (1.14, 1.91)[2]	0.88 (0.63, 1.25)	0.91 (0.61, 1.34)	0.89 (0.53, 1.51)
Seeds	1.24 (0.94, 1.64)	0.78 (0.53, 1.14)	0.72 (0.47, 1.12)	0.75 (0.42, 1.33)
Deep-frying vegetable fat	1.10 (0.87, 1.41)	1.25 (0.92, 1.70)	1.12 (0.79, 1.58)	1.61 (1.02, 2.54)[2]
Nuts	0.85 (0.63, 1.14)	0.92 (0.62, 1.34)	1.10 (0.72, 1.67)	0.84 (0.46, 1.53)
Fish	0.75 (0.57, 0.98)[2]	1.02 (0.73, 1.43)	1.01 (0.69, 1.48)	0.94 (0.56, 1.57)
Raw carrots	1.12 (0.85, 1.46)	0.85 (0.61, 1.18)	1.02 (0.69, 1.49)	0.77 (0.47, 1.28)
Spinach	1.26 (0.99, 1.61)	0.97 (0.71, 1.32)	0.82 (0.58, 1.17)	1.18 (0.73, 1.91)
Cabbage	1.24 (0.96, 1.59)	0.92 (0.66, 1.28)	0.84 (0.58, 1.22)	1.16 (0.71, 1.90)
Celery	0.94 (0.67, 1.31)	1.61 (1.07, 2.41)[2]	1.85 (1.18, 2.89)[2]	1.39 (0.74, 2.58)
Raw tomatoes	0.83 (0.63, 1.10)	0.81 (0.57, 1.16)	0.74 (0.49, 1.11)	1.05 (0.62, 1.77)
Raw sweet pepper	0.97 (0.75, 1.27)	1.45 (1.03, 2.06)[2]	1.16 (0.79, 1.69)	2.16 (1.20, 3.90)[2]
Salad	0.92 (0.69, 1.22)	1.09 (0.76, 1.57)	1.14 (0.76, 1.72)	0.92 (0.52, 1.62)
Vegetable juice	0.91 (0.68, 1.22)	0.78 (0.53, 1.16)	0.85 (0.56, 1.31)	0.85 (0.46, 1.56)
Citrus fruit	1.03 (0.78, 1.35)	1.82 (1.29, 2.56)[2]	1.73 (1.18, 2.53)[2]	1.72 (1.02, 2.92)[2]
Apples	0.92 (0.72, 1.21)	1.07 (0.77, 1.49)	1.01 (0.70, 1.46)	0.87 (0.52, 1.47)
Exotic fruit	0.85 (0.66, 1.11)	0.77 (0.55, 1.07)	0.84 (0.58, 1.23)	0.64 (0.39, 1.07)
Bananas	1.03 (0.77, 1.38)	1.08 (0.75, 1.55)	1.14 (0.75, 1.72)	1.10 (0.63, 1.93)
Strawberries	1.02 (0.77, 1.35)	1.06 (0.75, 1.51)	0.90 (0.60, 1.34)	1.46 (0.87, 2.47)
Fruit juice	1.18 (0.90, 1.54)	1.03 (0.73, 1.46)	1.12 (0.76, 1.65)	0.78 (0.47, 1.30)

[1] All values are odds ratios adjusted for study area, sex, maternal age at delivery, smoking during second or third trimester of pregnancy, parental education, exclusive breastfeeding for ≥4 mo, family history of atopy, season of birth, and all dietary variables. The low intake category was set as the reference group.
[2] $P < 0.05$.

toward the null value. Therefore, misclassification bias is unlikely to affect significant associations. Furthermore, we cannot completely rule out that the reported associations were modified by the diet of the children during the first 2 y of life. We estimated the correlation between maternal consumption frequencies of fish, celery, and citrus fruit during pregnancy and the time of introduction of these foods to the infant's diet during the first year of life. The correlation coefficients did not indicate a statistically significant association, but it might be possible that maternal food consumption frequencies are a surrogate marker of infant food consumption frequencies during the first 2 y of life. This would indicate that our findings might be at least partly a consequence of postnatal dietary influences. However, interventional trials are necessary to disentangle maternal diet from the diet of the child. Because many food items were grouped together in one category, it was not possible to evaluate the health effect of each single food, such as different kinds of nuts. Potential antagonistic effects of these foods might have masked some associations that might be especially relevant for allergenic foods. Furthermore, simultaneous adjustment for all dietary variables in the multiple logistic regression models might raise concern of overadjustment. We did not observe any substantial differences between the crude and adjusted models. Thus, it is unlikely that overadjustment affected our findings. One might also speculate that atopic mothers alter their diet during pregnancy and avoid known food allergens to prevent the onset of allergic diseases in their offspring. In this case, reverse causation might have been responsible for the observed associations. However, testing for interactions between food intake and maternal history of atopic diseases did not confirm the assumption that food intake during pregnancy is related to a higher risk of allergic diseases in the children of atopic mothers only. Because of a lack of statistical power, this study could not provide valid data to identify more specific associations between single foods and specific food sensitization. The possibility that significant associations occurred by chance as a result of multiple testing should also be kept in mind; however, because the observed significant effects mainly related to the initially proposed hypothesis, it is unlikely that the results might be explained by chance alone.

One of the major strengths of the present study was the large sample size, which enabled us to detect statistically significant associations, which are biologically plausible but have not been described previously. A prospective study design, as used in the present study, is certainly superior to a cross-sectional design for studying cause-effect relations.

In conclusion, these prospective data from a large cohort study indicate an association between maternal diet during pregnancy, particular foods rich in PUFAs and allergenic foods, and the risk of allergic diseases in the offspring. Currently, no recommendations are being made to mothers to modify their diets to prevent allergies in their children because of insufficient evidence of a beneficial effect. However, before any recommendations can be made, randomized clinical intervention trials should be performed to confirm the cause-effect relation observed in the present study.

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SS was responsible for the data analysis, interpretation of data, and manuscript preparation. SK and IL assisted with the interpretation of results and critical revision of the manuscript. MB, OH, BS, AvB, HEW, and JH were responsible for the data collection and assisted with the interpretation of results. SS and JH developed the design and analysis plan. None of the authors had a conflict of interest.

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APPENDIX A

Categories derived from the original food-frequency questionnaire (FFQ)

Category	Wording in the FFQ
Milk	Milk, buttermilk, kefir (fermented milk drink)
Yogurt	Yogurt, soured milk, curd
Cheese	Cheese, cream cheese
Cream	Cream, sour cream, heavy cream, coffee creamer
Eggs	Eggs
Butter	Butter
Margarine	Margarine
Vegetable oils	Vegetable oils (other than olive oil), eg, linseed oil, rapeseed oil, wheat germ oil, soybean oil, walnut oil, sunflower oil, safflower oil
Seeds	Oil seeds, eg, sesame, sunflower seeds, olives, coconut
Deep-frying vegetable fat	Solid vegetable cooking fat, eg, coconut oil, Palmin[1], Biskin[1]
Nuts	Nuts, eg, peanuts, walnuts, Brazil nuts, cashew nuts, pumpkin seeds
Fish	Fish
Raw carrots	Raw carrots
Spinach	Spinach, Swiss chard
Cabbage	Cabbage, eg, cauliflower, red cabbage, turnip cabbage, white cabbage, curly kale, savoy cabbage, Brussels sprouts, broccoli
Celery	Celery
Raw tomatoes	Raw tomatoes
Raw sweet pepper	Raw sweet pepper
Salad	Leaf salad, eg, chicory, endive, iceberg lettuce, lamb's lettuce, Chinese cabbage, dandelion greens
Vegetable juice	Vegetable juice, eg, sauerkraut, tomato, carrot, spinach, cucumber juice
Citrus fruit	Citrus fruit, eg, orange, grapefruit, lemon
Apples	Apples
Exotic fruit	Kiwi, fresh pineapple, mango
Bananas	Bananas
Strawberries	Strawberries
Fruit juice	Fruit juice, eg, apple, orange, tangerine, grapefruit juice

[1] Peter Kölln KGaA, Elmshorn, Germany.