

Margarine and butter consumption, eczema and allergic sensitization in children. The LISA birth cohort study

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It has been hypothesized that margarine intake is associated with allergic diseases. However, the epidemiological evidence in children is limited. The aim of the present study was to assess the relationship between dietary intake of margarine and butter with eczema and allergic sensitization in 2-yr-old children. Data of 2582 children at the age of 2 yr with complete information on exposure to diet and allergic outcome were analyzed in a German prospective birth cohort study (LISA). Margarine and butter intake were estimated from a semiquantitative food frequency questionnaire about general fat use at home combined with questions on the child's spread intake. Multiple logistic regression analysis was applied comparing predominant margarine and predominant butter intake with consumption of both butter and margarine. Predominant margarine intake was positively associated with lifetime prevalence of symptomatic eczema (aOR: 1.71; 95% CI: 1.12–2.61) and doctor-diagnosed eczema (aOR: 2.10; 95% CI: 1.36–3.25) and allergic sensitization against inhalant allergens (aOR: 2.10; 95% CI: 1.01–4.41) at the age of 2 yr. No statistically significant associations were found for butter intake. Stratification for parental history of atopic diseases indicated that children at high risk of atopic diseases have higher effect estimates for margarine intake compared to children without parental history of atopic diseases. Stratification for sex also showed higher effect estimates in boys. Children with predominant margarine consumption had an increased risk for eczema and allergic sensitization, while butter intake was no predictor for allergic diseases. However, we could not determine whether margarine is a causal risk factor or whether other lifestyle factors have influenced this association.

There is a wide consent that the prevalence of atopic diseases in children has been steadily rising over the past decades in countries with a western lifestyle such as Germany (1, 2), even though some recently published studies are reporting a plateau (3–6). In the context of increasing prevalence rates, it has been suggested that dietary factors might have contributed to this increasing trend. One of the most pronounced dietary changes is marked by the altered consumption of polyunsaturated fatty acids (PUFA), especially the elevated consumption of proinflammatory n-6

PUFA (7), which was also observed in terms of increased margarine consumption in East Germany after reunification (8). A diet rich in n-6 PUFA, such as linoleic acid (C18:2, n-6), has been proposed to influence the development of allergic sensitization by formation of arachidonic acid-derived prostaglandin E₂. This in turn promotes the production of IgE, which is associated with an increased risk for atopic diseases (9).

As n-6 PUFA are particularly contained in vegetable oils and margarine, several studies on

**Stefanie Sausenthaler¹,
Iris Kompauer^{1,2}, Michael Borte^{3,4},
Olf Herbarth^{5,6}, Beate Schaaf⁷,
Andrea von Berg⁷, Anne Zutavern^{1,2}
and Joachim Heinrich¹ for the LISA
Study Group***

¹GSF – National Research Centre for Environment and Health, Institute of Epidemiology, Neuherberg, ²Ludwig-Maximilians-University of Munich, Institute of Medical Data Management, Biometrics and Epidemiology, Munich, ³Department of Pediatrics, University of Leipzig, Leipzig, ⁴Municipal Hospital 'St. Georg' Leipzig, Children's Hospital, Leipzig, ⁵Department of Human Exposure Research and Epidemiology, UFZ – Centre for Environmental Research, Leipzig, ⁶Faculty of Medicine, Environmental Hygiene and Environmental Medicine, University of Leipzig, Leipzig, ⁷Department of Pediatrics, Marien-Hospital Wesel, Wesel, Germany

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Joachim Heinrich, GSF – Institute of Epidemiology, Ingolstaedter Landstr. 1, 85764 Neuherberg, Germany
Tel.: +49 89 3187 4150
Fax: +49 89 3187 3380
E-mail: joachim.heinrich@gsf.de

*Members of and institutions affiliated with the LISA Study Group are listed in Appendix.

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dietary risk factors for allergic diseases used margarine consumption substitutional for n-6 PUFA intake, while butter adequately acted as surrogate marker for saturated fatty acids. This way margarine intake has been linked to an increased risk (10, 11) and butter consumption to a decreased risk of atopic diseases in children (1, 10, 12).

However, most of these studies have focused on children older than 3 yr, although there is evidence that the immunocompetence mainly develops during very early childhood (13). Therefore, the aim of the present study was to assess, if predominant margarine or butter intake are associated with eczema and allergic sensitization in children at 2 yr of age.

Subjects and methods

Subjects

We analyzed data from the LISA study on 'Influences of lifestyle-related factors on the immune system and the development of allergies in childhood'. In this prospective birth cohort study, 3097 newborns whose mothers had completed a self-administered questionnaire on different lifestyle factors shortly after birth, were recruited between November 1997 and January 1999 in the four German cities Munich, Leipzig, Wesel and Bad Honnef (14). Only healthy full-term neonates of German parentage were included. Exclusion criteria have been described in detail elsewhere (15).

Data on the child's health and on lifestyle factors were collected by repeated parental-completed questionnaires at regular time intervals during the follow up of 2 yr (6, 12, 18 and 24 months of child's age). About 2664 subjects returned the 2-yr questionnaire (86% of the baseline population), and in 2176 children blood samples were drawn for total and specific immunoglobulin E (IgE) analysis. Information on butter and margarine consumption at age 2 yr was obtained from 2582 participants. Thus, a complete set of data from all questionnaires including exposure to diet was available for 2582 children.

The study protocol was approved by the local ethics committees and informed consent was obtained from the parents.

Outcome definition

Symptomatic eczema was defined as itchy rash that was not restricted to the skin underneath the diaper, and that was either recurrent or persisted

more than 14 days. Doctor-diagnosed eczema was based on a positive answer to the question: 'Has a doctor diagnosed an allergic or atopic eczema in your child in the past 6 months'? Finally, we used four different definitions for analysis. Lifetime prevalence of symptomatic and doctor-diagnosed eczema respectively was assumed, if eczema had ever appeared in the first 2 yr of life. Incidence of symptomatic and doctor-diagnosed eczema in the second year of life was defined as occurrence for the first time between the age of 1 and 2 yr, which is more closely related to exposure. These varied definitions in time provided an opportunity to evaluate the temporal relationship between diet exposure and outcome.

Because children in this study were only 2 yr old and rhinoconjunctivitis and asthma can hardly be established by that time (16), we analyzed neither of them. This was supported by small lifetime prevalence rates of doctor-diagnosed rhinoconjunctivitis (1.1%) and doctor-diagnosed asthma (0.5%).

Allergic sensitization at the age of 2 yr was assessed by measuring specific IgE to common food allergens (egg, cow's milk, wheat, peanut, soya bean, codfish) and to inhalant allergens (house dust mite, cockroach, cat, mixed grass, birch pollen, mixed moulds). IgE levels were determined using the Pharmacia system (Pharmacia, Freiburg, Germany) with a detection limit of 0.35 kU/l. A child with at least one specific IgE ≥ 0.35 kU/l (RAST 1) was considered to be sensitized. In addition, children were categorized according to food or inhalant sensitization.

Dietary assessment

Data on dietary intake were obtained at the age of 2 yr using a semiquantitative food frequency questionnaire. Parents were asked how often they have used butter and margarine respectively in the past 6 months for cooking and baking at home. The following six answers were possible: '(almost) daily', 'several times a week', 'about once a week', 'two to three times a month', 'once in a month or less' and '(almost) never'. We summarized these categories and established two main groups of frequent (more than once a week) and infrequent (once a week or less) consumption at home.

Furthermore, parents should specify the kind of spread they gave their child in the last 6 months: 'only butter', 'only margarine', 'more butter than margarine', 'more margarine than butter', 'the same amount of butter and

margarine', or 'neither of them'. We aggregated similar answering categories and distinguished between 'butter only', 'margarine only', 'butter and margarine' (in any case of combined spread) and 'neither butter nor margarine' in terms of the child's spread intake.

To avoid any loss of information concerning total intake of butter and margarine, we combined consumption frequencies at home and the child's spread intake. Therefore, we defined three mutually exclusive main exposure categories.

- (i) Butter group: Children with frequent butter and infrequent margarine consumption at home and who only receive butter for spread (N = 782).
- (ii) Margarine group: Children with frequent margarine and infrequent butter consumption at home and who only receive margarine for spread (N = 188).
- (iii) Mixed group: The remaining group (N = 1612).

The mixed group was used as reference group in the statistical analysis. This methodological approach warranted to contrast predominant margarine and predominant butter intake against the intake of both.

Statistical methods

Potential confounding factors were used to describe the study population according to the exposure categories. We further applied multiple logistic regression analysis to estimate the association between butter and margarine intake and eczema and allergic sensitization. Odds ratios (OR) with 95% confidence intervals (CI) were computed for the butter and the margarine group respectively compared with the reference group, controlling for potential confounders. The adjusted model included study area (Munich/Leipzig/Wesel/Bad Honnef), gender, maternal age at delivery (≤ 31 / > 31 yr), maternal smoking during second or third trimester of pregnancy, level of parental education (very high/high/medium/low), exclusive breast feeding for at least 4 months, parental history of atopic diseases (asthma, hay fever or eczema; none/one parent atopic/both parents atopic), fresh fruit intake ($\geq$ daily/ $<$ daily), salad and raw vegetable intake ($\geq$ daily/ $<$ daily), keeping a dog (yes/no) and keeping a cat (yes/no). Stratification was carried out for parental history of atopic diseases and gender.

All computations were performed by using the statistical analysis package sas for Windows version 8.2 (SAS Institute, Cary, NC, USA).

Results

Table 1 shows the basic characteristics of the study population according to the main exposure categories. About 782 (30.3%) of 2582 subjects predominantly consumed butter, while 188 (7.3%) children predominantly received margarine. By comparing the percentage of children between the different strata in each exposure group, substantial differences became apparent. Almost half of the children living in Munich predominantly consumed butter (47.2%), but only 1.3% predominantly consumed margarine, while children in Wesel, for example, favoured margarine (18.6%) over butter (8.4%). The proportion of children in the butter group was higher in children of mothers who were older than 31 yr at delivery (37.3% vs. 24.0%) and in children who were exclusively breastfed for at least 4 months (34.2% vs. 25.4%). Moreover, the frequency of predominant butter intake showed a clear trend to increase with increasing parental education, while predominant margarine intake was most prevalent in children whose parents had a lower education. Differences in maternal smoking during pregnancy and parental history of atopic diseases and eczema were also seen for predominant butter intake. Children with predominant margarine intake less likely reported eating salad and raw vegetables at least daily, and more likely kept cats or dogs in their home than children with predominant butter intake. In contrast, we could not observe any differences in gender, number of older siblings, birth weight, body mass index and fresh fruit intake.

The incidence rate of eczema in the second year of life was 9.7% for symptomatic eczema and 7.5% for doctor-diagnosed eczema in the study population. Lifetime prevalence was 20.9% for symptomatic eczema and 17.7% for doctor-diagnosed eczema. Sensitization against food allergens was more prevalent (9.3%) than sensitization against inhalant allergens (4.8%). Overall, 12.3% of the children were sensitized against any (food or inhalant) allergen.

Table 2 shows the prevalence rates in the different exposure categories. The incidence of symptomatic eczema in the second year was higher in the butter group (11.4%) than in the mixed (8.9%) and the margarine group (9.4%). The highest prevalence for all other outcome variables was seen in children with predominant margarine consumption. At the same time there was a large discrepancy between the frequency of reported symptoms and doctor-diagnosed eczema in the butter group, but not in the margarine group.

Table 1. Basic characteristics of the LISA study population at the age of 2 yr according to the main exposure category

Variable	N	Mixed group* (N = 1612)	Butter group† (N = 782)	Margarine group‡ (N = 188)
Total	2582	1612 (62.4)	782 (30.3)	188 (7.3)
Study area				
Munich	1285	661 (51.5)	607 (47.2)	17 (1.3)
Leipzig	772	586 (75.9)	94 (12.2)	92 (11.9)
Wesel	263	192 (73.0)	22 (8.4)	49 (18.6)
Bad Honnef	262	173 (66.0)	59 (22.5)	30 (11.5)
Gender				
Male	1327	827 (62.3)	410 (30.9)	90 (6.8)
Female	1255	785 (62.6)	372 (29.6)	98 (7.8)
Maternal age at delivery (yr)				
≤ 31	1352	898 (66.4)	324 (24.0)	130 (9.6)
> 31	1228	712 (58.0)	458 (37.3)	58 (4.7)
Maternal smoking during pregnancy§				
No	2223	1370 (61.6)	696 (31.3)	157 (7.1)
Yes	246	165 (67.1)	57 (23.2)	24 (9.7)
Level of parental education				
Very high	1392	819 (58.8)	525 (37.7)	48 (3.5)
High	526	341 (64.8)	134 (25.5)	51 (9.7)
Medium	509	350 (68.8)	95 (18.6)	64 (12.6)
Low	126	84 (66.6)	21 (16.7)	21 (16.7)
Exclusively breastfed for at least 4 months				
Yes	1468	889 (60.6)	503 (34.2)	76 (5.2)
No	1086	699 (64.4)	276 (25.4)	111 (10.2)
Parental history of atopic diseases¶				
None	1216	786 (64.7)	325 (26.7)	105 (8.6)
One parent atopic	1015	621 (61.2)	333 (32.8)	61 (6.0)
Both parents atopic	346	204 (58.9)	121 (35.0)	21 (6.1)
Parental history of eczema				
No	2046	1283 (62.7)	608 (29.7)	155 (7.6)
Yes	351	212 (60.4)	124 (35.3)	15 (4.3)
Number of older siblings				
0	1456	898 (61.7)	452 (31.0)	106 (7.3)
1	873	547 (62.7)	257 (29.4)	69 (7.9)
≥ 2	253	167 (66.0)	73 (28.9)	13 (5.1)
Birth weight (g)				
2500–3249	816	505 (61.9)	256 (31.4)	55 (6.7)
3250–3649	876	567 (64.7)	258 (29.5)	51 (5.8)
3650–5200	890	540 (60.7)	268 (30.1)	82 (9.2)
Body mass index**				
Normal weight	2414	1513 (62.7)	728 (30.1)	173 (7.2)
Overweight	155	91 (58.7)	50 (32.3)	14 (9.0)
Obesity	13	8 (61.5)	4 (30.8)	1 (7.7)
Fresh fruit intake				
≥ daily	2034	1260 (61.9)	638 (31.4)	136 (6.7)
< daily	512	327 (63.9)	137 (26.8)	48 (9.3)
Salad and raw vegetable intake				
≥ daily	753	473 (62.8)	249 (33.1)	31 (4.1)
< daily	1553	966 (62.2)	455 (29.3)	132 (8.5)
Keeping a cat				
Yes	262	167 (63.7)	57 (21.8)	38 (14.5)
No	2193	1365 (62.2)	694 (31.7)	134 (6.1)
Keeping a dog				
Yes	204	133 (65.2)	47 (23.0)	24 (11.8)
No	2251	1399 (62.1)	704 (31.3)	148 (6.6)

Values are given as n (%).

*All combinations of butter and margarine consumption and spread intake except for which are listed in footnotes † and ‡.

†Butter more than once a week, margarine once a week or less, spread: butter only.

‡Margarine more than once a week, butter once a week or less, spread: margarine only.

§During second or third trimester.

¶Asthma, hay fever or eczema.

**Body mass index according to Cole et al. (17) for boys (girls) at the age of 2 yr: normal weight: < 18.41 (18.02) kg/m² (equal to adult BMI < 25.0 kg/m²); overweight: 18.41–20.07 (18.02–19.80) kg/m² (equal to adult BMI 25.0–29.9 kg/m²); obesity ≥ 20.08 (19.81) kg/m² (equal to adult BMI ≥ 30.0 kg/m²).

Table 2. Prevalence rates for eczema and allergic sensitization in the LISA study population at the age of 2 yr stratified for main exposure categories

Variable	Mixed group* (N = 1612)		Butter group† (N = 782)		Margarine group‡ (N = 188)	
	n/N	%	n/N	%	n/N	%
Eczema symptoms						
Incidence in the second year of life	115/1297	8.9	73/639	11.4	13/139	9.4
Lifetime prevalence	297/1479	20.1	151/717	21.1	47/173	27.2
Doctor-diagnosed eczema						
Incidence in the second year of life	99/1375	7.2	53/678	7.8	13/137	9.5
Lifetime prevalence	262/1538	17.0	129/754	17.1	45/169	26.6
Allergic sensitization§ against						
food or inhalant allergens	158/1315	12.0	73/631	11.6	26/151	17.2
food allergens	120/1322	9.1	57/631	9.0	18/151	11.9
inhalant allergens	59/1314	4.5	27/631	4.3	14/151	9.3

*All combinations of butter and margarine consumption and spread intake except for which are listed in footnotes † and ‡.

†Butter more than once a week, margarine once a week or less, spread: butter only.

‡Margarine more than once a week, butter once a week or less, spread: margarine only.

§IgE ≥0.35 kU/l.

Results from multiple logistic regression analysis are presented in Table 3. For all response variables of eczema and allergic sensitization the risk was higher in infants with predominant margarine consumption compared with the mixed consumption group, even though statistical significance was only reached for lifetime prevalence of symptomatic eczema (aOR: 1.71; 95% CI: 1.12–2.61) and doctor-diagnosed eczema (aOR: 2.10; 95% CI: 1.36–3.25), and for allergic sensitization against inhalant allergens (aOR: 2.10; 95% CI: 1.01–4.41). No statistically significant associations were found for butter intake and any of the outcome variables.

Stratification by family history of atopic diseases showed that the increased effect estimates in the group of predominant margarine consumption were mainly attributed to children with atopic parents (Table 4). Butter consuming children with a positive parental history of atopic diseases had slightly higher effect estimates than children without parental history of atopic diseases. However, only the association between butter intake and incidence of symptomatic eczema in the second year of life was statistically significant in children with atopic parents.

Sex-stratified regression analysis indicated that significant associations existed in boys, but not in girls (data not shown). Even though for some outcome variables the ORs for margarine intake were increased in both sexes, statistical significance was only reached in boys for lifetime prevalence of symptomatic eczema (aOR: 2.04; 95% CI: 1.11–3.76) and doctor-diagnosed eczema (aOR: 3.11; 95% CI: 1.68–5.76), incidence of doctor-diagnosed eczema in the second year (aOR: 2.92; 95% CI: 1.08–7.94) and allergic

Table 3. Crude and adjusted associations between outcomes and main exposure categories of butter and margarine consumption in the LISA study population at the age of 2 yr

Variable	Mixed group* (N = 1612)		Butter group† (N = 782)		Margarine group‡ (N = 188)	
	OR		OR (95% CI)		OR (95% CI)	
Eczema symptoms						
Incidence in the second year of life						
OR§	1.00		1.33 (0.97–1.81)		1.06 (0.58–1.94)	
aOR¶	1.00		1.29 (0.89–1.88)		1.30 (0.67–2.55)	
Lifetime prevalence						
OR§	1.00		1.06 (0.85–1.32)		1.49 (1.04–2.13)	
aOR¶	1.00		1.05 (0.80–1.37)		1.71 (1.12–2.61)	
Doctor-diagnosed eczema						
Incidence in the second year of life						
OR§	1.00		1.09 (0.77–1.55)		1.35 (0.74–2.48)	
aOR¶	1.00		1.02 (0.68–1.55)		1.70 (0.84–3.41)	
Lifetime prevalence						
OR§	1.00		1.01 (0.80–1.27)		1.77 (1.23–2.55)	
aOR¶	1.00		0.97 (0.74–1.29)		2.10 (1.36–3.25)	
Allergic sensitization** against						
food or inhalant allergens						
OR§	1.00		0.96 (0.71–1.29)		1.52 (0.97–2.40)	
aOR¶	1.00		0.98 (0.68–1.39)		1.52 (0.89–2.58)	
food allergens						
OR§	1.00		1.00 (0.72–1.38)		1.36 (0.80–2.30)	
aOR¶	1.00		1.03 (0.69–1.55)		1.58 (0.87–2.86)	
inhalant allergens						
OR§	1.00		0.95 (0.60–1.52)		2.17 (1.18–4.00)	
aOR¶	1.00		1.00 (0.57–1.72)		2.10 (1.01–4.41)	

*All combinations of butter and margarine consumption and spread intake except for which are listed in footnotes † and ‡.

†Butter more than once a week, margarine once a week or less, spread: butter only.

‡Margarine more than once a week, butter once a week or less, spread: margarine only.

§Crude odds ratios.

¶Odds ratios adjusted for study area, gender, maternal age at delivery, maternal smoking during second/third trimester of pregnancy, level of parental education, exclusive breast feeding during the first 4 months, family history of atopic diseases, fresh fruit intake, salad and raw vegetable intake, keeping a dog, keeping a cat.

**IgE ≥0.35 kU/l.

Table 4. Adjusted associations between outcomes and main exposure categories of butter and margarine consumption in the LISA study population at the age of 2 yr stratified by family history of atopic diseases

Variable	Negative family history of atopic disease (N = 1216) ¹		Positive family history of atopic disease (N = 1361) ¹	
	Butter group† (N = 325) aOR¶ (95% CI)*	Margarine group‡ (N = 105) aOR¶ (95% CI)*	Butter group† (N = 454) aOR¶ (95% CI)*	Margarine group‡ (N = 82) aOR¶ (95% CI)*
Eczema symptoms				
Incidence in the second year of life	0.69 (0.34–1.37)	1.26 (0.52–3.09)	1.78 (1.11–2.84)	1.17 (0.41–3.35)
Lifetime prevalence	0.99 (0.48–2.02)	0.67 (0.19–2.32)	1.07 (0.64–1.79)	3.32 (1.35–8.16)
Doctor-diagnosed eczema				
Incidence in the second year of life	0.87 (0.55–1.38)	1.68 (0.92–3.08)	1.16 (0.83–1.62)	1.71 (0.94–3.12)
Lifetime prevalence	1.05 (0.64–1.72)	1.26 (0.63–2.51)	0.97 (0.69–1.35)	3.21 (1.78–5.81)
Allergic sensitization§ against				
food or inhalant allergens	0.63 (0.34–1.18)	1.06 (0.48–2.36)	1.26 (0.81–1.96)	2.41 (1.15–5.05)
food allergens	0.69 (0.34–1.41)	1.37 (0.58–3.20)	1.28 (0.77–2.11)	2.09 (0.89–4.89)
inhalant allergens	0.75 (0.27–2.07)	0.79 (0.21–3.00)	1.24 (0.63–2.42)	4.10 (1.56–10.76)

*Mixed group was used as reference category.

†Butter more than once a week, margarine once a week or less, spread: butter only.

‡Margarine more than once a week, butter once a week or less, spread: margarine only.

§IgE ≥0.35 kU/l.

¶Odds ratios adjusted for study area, gender, maternal age of delivery, maternal smoking during second/third trimester of pregnancy, level of parental education, exclusive breast feeding during the first 4 months, fresh fruit intake, salad and raw vegetable intake, keeping a dog, keeping a cat.

sensitization against inhalant allergens (aOR: 2.93; 95% CI: 1.22–7.08).

Restricting the analysis to children who have not avoided dairy products in the last 6 months, somewhat decreased the magnitude of the effect estimates, but did not alter the significance level (data not shown).

Discussion

This study suggests a positive association between margarine intake and eczema and allergic sensitization in children at the age of 2 yr. These results are consistent with most of the other observational studies in children. However, we found no association between butter intake and eczema or allergic sensitization.

In a study investigating time trends in East Germany between 1991/1992 and 1995/1996, von Mutius et al. found a positive association between an increased margarine consumption and prevalence of hay fever, and an inverse relationship between increased butter intake and hay fever and atopic sensitization among school-children at the age of 9–11 yr (1). Another cross-sectional study conducted in Germany compared 5–14-yr-old children with respect to the type of fat they used as spread. Boys with exclusive margarine consumption had a higher risk for allergic sensitization and rhinitis symptoms compared to those with exclusive butter consumption. No associations were found for either doctor-diagnosed hay fever or asthma or allergic diseases in girls (11). In Finland, Dunder et al. employed a 48 h recall to assess dietary fat intake

in children aged 3–18 yr. They analyzed the data in two different ways. In view of the longitudinal data, they could show that children, who developed atopic disease during the follow up of 9 yr, had consumed less butter before the expression of atopic disease. According to the cross-sectional data, children with atopic diseases consumed more margarine and less butter than non-atopic children did (10).

Two investigations on respiratory symptoms in children estimated dietary margarine and butter intake by means of a semiquantitative food frequency questionnaire. In an Italian study, consumption of bread with margarine was associated with wheeze and consumption of bread with butter with shortness of breath with wheeze (18). A Dutch birth cohort study found an inverse association between daily butter consumption and asthma and wheeze in pre-school children (12). Further evidence for both the increased risk of margarine consumption (19, 20) and the protective effect of butter consumption (21) is published by studies on asthma in adults. In our study, there was no clear evidence for any association between butter consumption and eczema and allergic sensitization.

In search of a biological mechanism, mainly two hypotheses have been discussed. Comparing the fatty acid composition of margarine and butter, margarine contains 10 to almost 30 times more linoleic acid than butter (22). This could partly explain the negative impact of margarine and the neutral effect of butter for allergic diseases in our study population. Besides n-6

PUFA, *trans*-fatty acids have been linked to increase the prevalence of allergic diseases (23). In Germany, the content of *trans*-fatty acids in vegetable oil margarine (2.8%), dietetic margarine (0.4%) and margarine semifat (0.8%) is not higher than in ordinary butter (2.8%; 22). At the same time linkage with food consumption data revealed that butter contributes about 50% to the total intake of *trans*-fatty acids in German households (24). Therefore, it is not obvious why margarine consumption, but not butter consumption should increase the risk for atopic diseases when considering *trans*-fatty acids.

Stratified multiple logistic regression analysis revealed the higher effect estimates for margarine intake to be mainly attributed to children with family history of atopic diseases. As studies on cardiovascular disease described (25), genetic polymorphisms encoding enzymes could change the metabolism of fatty acids. This may explain the variability on the effects of margarine intake on atopy between subjects with and without family history of atopic diseases. This hypothesis is supported by observations indicating that patients with atopic diseases, especially eczema (26), have deviating serum fatty acid compositions (27). Abnormal fatty acid compositions were also seen in the cord blood of newborns at high risk of atopic diseases (28).

Genetic influence could also explain the effect modification by sex when analysing separately for boys and girls. As previously reported (11), the associations in our study population between margarine consumption and allergic disease in sex-stratified analysis were mainly limited to boys. Effects of polymorphisms involved in fat metabolism have been shown to depend on sex (29). In this way, gender-specific effects of genotype on fatty acid metabolism could be responsible for the higher susceptibility to allergic diseases in boys consuming margarine. In any case, the results of the stratified analysis have to be interpreted with great caution because of small numbers in each stratum and as formal testing for interaction did not show significant differences between boys and girls.

There are several important aspects when interpreting the findings of this study. First, we did not have adequate data to prove the hypothesis of n-6 PUFA being associated with allergic diseases. On the one hand, other sources of PUFAs would have had to be taken into account, because it has been shown that in addition to fats and vegetable oils other products vastly contribute to the total intake of PUFAs (24). On the other hand, we even could

not consider brand-related differences in fatty acid composition of butter and margarine. Thus, we were not able to demonstrate an association between butter or margarine and allergic diseases based on biological mechanism.

In addition, total spread intake in children at age 2 yr is probably not very high. Therefore, we combined consumption frequencies of cooking and baking at home with the spread use of the child in one exposure variable. Assuming that household consumption frequencies can be used as a surrogate for the diet of the child, this provides a more precise insight into the actual intake of margarine and butter.

Furthermore, it would be possible that the findings partly depend on reverse causation. A recent recommendation suggested an oligo-allergenic diet, if food allergy is suspected in patients with eczema. This diet also includes milk-free margarine (30). In our study population, children with predominant margarine consumption avoided dairy products nearly twice as much as children in the butter group did (14.4% vs. 7.9%). As effect estimates in multivariate analysis were lowered when excluding those who deliberately avoided dairy products, the association between predominant margarine consumption and eczema could also reflect altered dietary patterns owing to the diagnosis. A second sensitivity analysis showed that parents with atopic diseases (8.3%) more frequently indicated to leave dairy products out of the child's diet than parents without atopic diseases (4.2%). Thus, children with allergic diseases might consume more margarine than healthy children, because atopic parents have restricted the diet of their child to prevent or to delay the outbreak of allergic diseases.

In this context, the temporal relationship between exposure and outcome should be thoroughly ascertained. Effect estimates of lifetime prevalence rates were consistently higher than for incidence rates in the second year of life, meaning that children in the margarine group would have a higher risk to develop eczema in the first year of life than in the second year. As we have analyzed margarine intake from age 1½ to 2 yr, no temporal relationship can be established for children who developed eczema in the first year. Therefore, margarine intake in children alone could not completely explain the higher effect estimates.

Assuming that the diet of children can be used as a surrogate for the diet of their parents, a prenatal influence of the mother's diet has to be taken into consideration because of the fact that

we showed margarine to be stronger related to early onset of eczema. In the setting of studies on maternal nutrition during pregnancy and breast feeding, the assessment of maternal margarine intake in a future study would help to determine if there are any significant effects on the development of atopic diseases in children.

One further discussion point is the discrepancy we observed between reported symptoms and doctor diagnosis of eczema, which has already been described in some former publications. For example, a Swedish study demonstrated that the diagnosis of atopic dermatitis based on parental evaluation could not be verified by dermatologists in one-third of the cases (31). Why this discrepancy was not existent within children in the margarine group and more pronounced in children from the butter group compared with the mixed group could not be finally clarified. As we have shown that the butter group had reached the highest educational levels, we suspect that these parents might be more health conscious than parents in the margarine group are. They might report eczema symptoms more likely and thus, in reality symptoms may be more frequent in the margarine group than those subjects evaluate.

However, none of these approaches could completely explain the results of our study. There could have been other factors we have not taken into account that influenced the observed associations. As the selection of lifestyle factors included in our multivariate analysis was arbitrary, these factors were consequently not considered as being causal or were they linked with any biological hypothesis. Thus, we just treated them as indicators of lifestyle. Smoking is one of the key determinants of health (32), which was related to margarine intake in our study population. Almost twice as many mothers of children in the margarine group as mothers of children in the butter group had been smoking during pregnancy. Furthermore, it is well documented that subjects of a lower socioeconomic status consume a less healthy diet, particularly less fruits and vegetables (33–35). In our study population, children of parents with low levels of education less likely consumed salad and raw vegetables and at the same time more likely consumed margarine than children of higher educated parents did.

These complex interrelations indicate that the associations between margarine intake and eczema and allergic sensitization are influenced by several determinants related to lifestyle, while margarine acts as an indicator for lifestyle.

In conclusion, we observed a positive relationship between margarine intake and eczema and allergic sensitization in 2-yr-old children in a large prospective birth cohort. Even though similar associations have already been reported before, this study contributes additional information on the modifying effect of parental atopy at this very early age. There are several possible explanations for the mechanism behind, but we could not disentangle the multitude of interacting factors. Therefore, it remains uncertain whether the associations are due to a causal role of dietary components of margarine or a less healthy lifestyle characterized by margarine consumption, which in turn enhances the susceptibility for allergic diseases or depend on reverse causation.

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Appendix

LISA Study Group: GSF – National Research Center for Environment and Health, Institute of Epidemiology, Neuherberg (Wichmann HE, Heinrich J, Bolte G, Belcredi P, Jacob B, Schoetzel A, Mosetter M, Schindler J, Höhnke A); Department of Pediatrics, University of Leipzig (Borte M, Schulz R, Sierig G, Mirow K, Gebauer C, Schulze B, Hainich J); Institute of Clinical Immunology and Transfusion Medicine (Sack U, Emmrich F); Department of Pediatrics, Marien-Hospital Wesel (von Berg A, Schaaf B, Scholten C, Bollrath C); Department of Human Exposure Research and Epidemiology, UFZ – Centre for Environmental Research Leipzig-Halle Ltd (Herbarth O, Diez U, Lehmann I, Rehagen M, Schlink U); Ludwig-Maximilians-University Munich, Dr von Haunersches Kinderspital, Division of Pediatric Infectious Diseases and Immunology (Weiss M, Albert M); Friedrich-Schiller-University Jena, Institute of Clinical Immunology (Fahlbusch B); Institute of Occupational, Social and Environmental Medicine (Bischof W, Koch A).