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Food diversity during the first year of life and allergic diseases until 15 years

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Capsule summary: Higher food diversity during the first year of life appears to decrease the risk of allergic sensitization to aeroallergens up to 15 years only among children with early skin symptoms in German birth cohort.

Key words: food diversity; eczema; asthma; allergic rhinitis; allergic sensitization; children

47 ***To the Editor:***

48 Contrary to current recommendations, several clinical trials in high risk children reported that
49 early introduction of highly allergenic foods, especially peanut and egg, prevents food allergy
50 later in life.^{1,2} This opened the debate about changing the recommendations about timing of
51 solid food introduction and length of exclusive breastfeeding to prevent allergic diseases.^{1,3}

52 Exposure to food antigens and bacteria has been suggested to modulate immune tolerance,
53 crucial for later development of allergic diseases.⁴ Therefore, not only timing of solid food
54 introduction, but also solid food diversity has become of research interest. So far, only a
55 handful of studies have addressed the latter issue specifically.⁵⁻⁸ Two studies have concluded
56 that higher food diversity during the first year of life might be protective against later
57 development of allergic diseases in children.^{5,6} However, in the first study,⁵ stratified
58 analyses indicated that associations with atopic asthma, allergic rhinitis and wheeze were
59 mainly present in a subgroup of children with atopic eczema. In the second study,⁶ an
60 association with asthma was no longer observed after exclusion of children with extremely
61 low food diversity. Both studies are based on selected populations and were not able to
62 sufficiently control for reverse causality.

63 In previous analyses of our own data from the population-based German birth cohort
64 LISAplus (recruited from 1998 to 1999) we looked at food diversity within the first six
65 months of life in association with allergic outcomes until 2 and 6 years. We found protective
66 effects for allergic sensitization to food allergens and eczema that are due to reverse causality.
67^{7,8} Here, we expanded the follow-up of LISAplus until age of 15 years. This led to bigger
68 numbers of cases and allowed longitudinal modelling with repeated assessments of five
69 allergic outcomes - doctor diagnosed eczema, asthma and allergic rhinitis, as well as
70 sensitization to aeroallergens and food allergens. We used several definitions of food

diversity (food group and food item diversity, each treated in quartiles and continuously) during the first year of life. All analyses were stratified by presence of a wide range of early skin symptoms to test the impact of reverse causality. The LISApplus cohort has been approved by the local ethics committees, and informed consent was obtained from all families. Study methods are described in Online Supplement S1 and a flow chart of study participants is provided in Fig. S1.

Participants with early skin symptoms (n=1507) differed from those without (n=1011) in many characteristics: they were more likely to be recruited in the big cities of Munich and Leipzig than in the small towns of Bad Honnef and Wesel, to have atopic parents or siblings as well as parents with higher education level, not to be exposed to tobacco smoke in utero or at home, and not to have older siblings (Table S1). Moreover, participants with early skin symptoms were more likely to have lower food diversity and higher prevalence of all five allergic outcomes.

In the total population, children in the highest quartile that were introduced to all eight food groups during the first year of life had lower odds of developing eczema up to 15 years compared to children in the lowest quartile with a maximum of five food groups (odds ratio=0.67 [95% confidence interval=0.48 to 0.94]; Table 1). The association was gone after stratification by early skin symptoms. Children in the highest quartile of food group diversity had lower odds of allergic sensitization to aeroallergens (0.61 [0.44 to 0.85]). This association was also present in children with early skin symptoms but not in those without. Except for an association with asthma (0.21 [0.05 to 0.82]), children without early skin symptoms showed no statistically significant associations. When food group diversity was treated as a continuous variable, statistically significant associations were observed for eczema in the total population and for allergic sensitization to aeroallergens in the total population and in

children with early skin symptoms. In sensitivity analyses (additionally adjusted models, restriction to participants with complete outcome data and restriction to participants with complete exposure data), the associations remained most consistent for allergic sensitization to aeroallergens. No age-varying effects of food group diversity during the first year were identified.

When food *item* diversity was used as an exposure variable instead of food group diversity, similar associations for allergic sensitization to aeroallergens were observed (Table S2). However, in children without early skin symptoms, high food item diversity increased risk of allergic rhinitis (third vs lowest quartile: 2.12 [1.04 to 4.29]).

At first glance, the results of our analyses seem to indicate that exposing children with early skin symptoms to higher diversity of food groups and items would lower their risk of allergic sensitization to aeroallergens. However, children with early skin symptoms are heterogeneous in terms of symptoms severity. Children with more severe symptoms are more likely to be forced into dietary restrictions. We can speculate that the subgroup with the most severe symptoms had the lowest food diversity while at the same time being at the highest risk of developing allergic sensitization later in life.⁹ Using this low-food-diversity, high-allergy-risk subgroup as a reference category predetermines the slope of the regression curve and gives the false impression that higher food diversity is protective against allergic sensitization to aeroallergens in children with early skin symptoms.

Other observed statistically significant associations are most likely due to chance which is supported by their inconsistency when using different definitions of food diversity and by several sensitivity analyses. Lack of statistical power might be another explanation for such inconsistency, especially in case of asthma where a very strict definition was used.

Large population size and longitudinal analysis of prospectively collected data on food diversity and several allergic outcomes, as well as the availability of detailed information on potential confounders are the main strengths of this study. Still, we did not have information on frequency or amount of introduced food items which is a clear limitation. Furthermore, we had very detailed information on early skin symptoms, which allowed us to accurately stratify the analyses and thereby minimize reverse causality in the subgroup without early skin symptoms. Nevertheless, we acknowledge that no observational study can rule out confounding and reverse causality completely, and therefore, randomized interventional studies are needed to further investigate the impact of food diversity on allergic diseases.³

In summary, higher food diversity during the first year of life appears to be associated with decreased risk of allergic sensitization to aeroallergens up to 15 years among children with early skin symptoms in our population-based cohort. The relevance of this observation is unclear.

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Author contributions

IM conducted the analyses, interpreted the data, drafted the initial manuscript, and revised the manuscript. MS and JH also contributed to the design of the analysis. IL, AvB, MS and JH contributed to the data collection, interpreted the data, reviewed and revised the manuscript. All authors approved the final manuscript as submitted and agree to be accountable for this work.

Conflict of interests

None.

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Table 1. Adjusted odds ratios with 95% confidence intervals of **diversity of food groups during the first 1 year** and a range of allergic outcomes up to 15 years of life estimated by generalized estimating equations models. All models are adjusted for time of follow-up, sex, study area, family history of allergic diseases, breastfeeding during the first four months and parental education.

	Total study population (n=2518)	Participants without early skin symptoms (n=1011)	Participants with early skin symptoms (n=1507)
Eczema (2-15 years)			
Diversity of food groups, quartiles			
0-5	1	1	1
6	0.79 (0.56-1.11)	1.31 (0.61-2.83)	0.86 (0.59-1.26)
7	0.80 (0.57-1.11)	1.07 (0.50-2.31)	0.95 (0.65-1.38)
8	0.67 (0.48-0.94)¹	1.25 (0.60-2.62)	0.68 (0.46-1.01)
Diversity of food groups, continuous [§]	0.90 (0.83-0.98)	1.02 (0.85-1.22)	0.91 (0.82-1.01)
Asthma (3-15 years)			
Diversity of food groups, quartiles			
0-5	1	1	1
6	1.15 (0.62-2.14)	0.57 (0.14-2.29)	1.41 (0.71-2.81)
7	0.91 (0.48-1.72)	0.73 (0.19-2.78)	1.02 (0.49-2.11)
8	0.53 (0.26-1.06)	0.21 (0.05-0.82)¹	0.70 (0.32-1.50)
Diversity of food groups, continuous [§]	0.89 (0.77-1.03)	0.82 (0.60-1.11)	0.94 (0.80-1.11)
Allergic rhinitis (3-15 years)			
Diversity of food groups, quartiles			
0-5	1	1	1
6	0.96 (0.65-1.42)	1.48 (0.65-3.41)	0.89 (0.57-1.39)
7	0.93 (0.64-1.34)	1.64 (0.76-3.55)	0.78 (0.51-1.21)
8	0.75 (0.51-1.12)	0.99 (0.42-2.38)	0.73 (0.46-1.14)
Diversity of food groups, continuous	0.94 (0.86-1.04)	1.01 (0.84-1.22)	0.93 (0.83-1.04)
Allergic sensitization to aeroallergens (at 6, 10 and 15 years)			
Diversity of food groups, quartiles			

0-5	1	1	1
6	1.05 (0.75-1.46)	0.98 (0.52-1.86)	1.04 (0.70-1.55)
7	0.84 (0.61-1.16)	0.86 (0.46-1.58)	0.80 (0.54-1.20)
8	0.61 (0.44-0.85)⁴	0.80 (0.44-1.43)	0.50 (0.30-0.83)²
Diversity of food groups, continuous [§]	0.88 (0.80-0.95)	0.93 (0.78-1.10)	0.82 (0.74-0.92)
Allergic sensitization to food allergens (at 6, 10 and 15 years)			
Diversity of food groups, quartiles			
0-5	1	1	1
6	1.39 (0.92-2.08)	1.45 (0.66-3.17)	1.46 (0.90-2.36)
7	1.15 (0.77-1.72)	1.41 (0.66-2.98)	1.07 (0.66-1.75)
8	1.14 (0.76-1.72)	1.49 (0.68-3.27)	1.02 (0.62-1.67)
Diversity of food groups, continuous [§]	1.03 (0.93-1.14)	1.11 (0.91-1.35)	0.99 (0.87-1.12)

Significant associations (p<0.05) are written in bold font.

¹ identifies that an effect estimate remained statistically significant in 1 out of 4 sensitivity analyses (additionally adjusted for early skin symptoms (total population only), additionally adjusted for birth weight, presence of older siblings, maternal smoking during pregnancy and tobacco smoke exposure in the home, exclusion of participants with partially missing outcome data, exclusion of participants with partially missing exposure data), ² – in 2 out of 4 sensitivity analyses, ³ – in 3 out of 4 sensitivity analyses, ⁴ – in 4 out of 4 sensitivity analyses (total population only).

[§] Odds ratio scaled per interquartile range increase (2 groups).

1 Supplemental material S1. Methods

2 **Study population.** Data were obtained from the ongoing multicentre population-based
3 German birth cohort LISAplus (Influence of Life-Style Factors on the Development of the
4 Immune System and Allergies in East and West Germany plus the Influence of Traffic
5 Emissions and Genetics).^{1,2} Briefly, healthy full-term neonates with a normal birth weight
6 were recruited at selected maternity hospitals in Munich, Leipzig, Wesel and Bad Honnef
7 between 1997 and 1999 (n=3094). Parent-completed questionnaires were administrated at
8 birth and when a child was six, 12 and 18 months, and two, four, six, 10 and 15 years old.
9 Additionally, at age of two, six, 10 and 15 years, blood samples were collected from a subset
10 of children. The LISAplus cohort has been approved by the local ethics committees, and
11 informed consent was obtained from all families.

12 **Food diversity.** Timing of introduction of 48 solid food items into child's diet was collected at
13 six months and at one year of age. If a family participated in both six months and one year
14 follow-up, and if the information on solid food introduction was partially answered, the
15 missing data were coded as being a report of not yet introduced food item.

16 48 food items were grouped into eight food groups: (1) vegetables (avocado, cauliflower,
17 beans, broccoli, peas, cucumbers, carrots, potatoes, white cabbage, turnip cabbage, lenses,
18 celery, asparagus, spinach, tomatoes, onion, vegetable juices); (2) fruit (apples, pineapples,
19 apricots, bananas, pears, strawberries, peaches, citrus fruit, fruit juices); (3) cereal
20 (bread/pretzels/rolls, cookies/cakes/rusk, rolled oats, muesli, millet, cornmeal/corn starch,
21 wheat semolina/starch, noodles, rice/rice starch, spelt); (4) meat (poultry, lamb, veal/beef,
22 pork, sausages); (5) egg; (6) dairy products (cow milk/cream, yoghurt/quark/cheese); (7) fish;
23 (8) other (nuts, soy products, cocoa/chocolate).^{1,2}

Food group diversity in child's diet during the first year of life was determined by summing up and subsequent categorization into quartiles according to the statistical distribution in the complete study population (regression results presented in Table 1). Additionally, food group diversity was analyzed continuously. As a sensitivity analysis, *food item diversity* at the first year of life was created (regression results presented in Table S2) to test whether results are subject to decisions made during data analysis.

Allergic outcomes. Data on allergic outcomes were collected at six, 12 and 18 months, and two, four, six, 10 and 15 years of age. In case of eczema, only information collected from two years onwards was used as an outcome; earlier information has been used as a part of the "early skin symptoms" definition to take into account potential reverse causation in the regression analyses. For other allergic outcomes, only information collected from three years onwards was used due to difficulty of accurate diagnosis of these outcomes at very young ages.

A doctor diagnosis of eczema (yearly, 2 to 15 years) and asthma (yearly, 3 to 15 years) was defined as a positive response to "In the last 12 months, has your child been diagnosed with eczema/asthma?" A doctor diagnosis of allergic rhinitis (yearly, 3 to 15 years) was defined as a positive response to one of the two questions "In the last 12 months, has your child been diagnosed with hay fever/allergic rhinitis?" If the follow-up period covered a timeframe of greater than one year, the prevalence of the diagnosis was asked separately for each year.

Specific immunoglobulin E (IgE) against common allergens was assessed at ages six, 10 and 15 years using the standardized CAP-RAST FEIA method (ThermoFischer, Freiburg, Germany). Allergic sensitization to common aeroallergens (SX1: house dust mites, cats, dogs, mold, birch, rye, mugwort and timothy grass) as well as allergic sensitization to food allergens

(FX5: milk, peanut, eggs, soya, cod, wheat flour) was defined as a specific IgE value above 0.35 kU/L against SX1 and FX5 allergens, respectively, in one or more blood samples.

Early skin symptoms. Early skin symptoms during the first year of life were determined as a doctor diagnosis of any of the following: atopic dermatitis, allergic or atopic eczema; food allergy, hives, urticaria, allergic edema; milk crust or seborrheic eczema; eczema without further specifications, or if parents reported eczema as a result of food intolerance or symptomatic allergic eczema. ¹ Missing data were coded as a report of no symptoms.

Statistical analysis. Given the longitudinal data structure (i.e. repeated assessment of allergic outcomes), generalized estimation equations (GEE) ³ with logit link and exchangeable correlation structure were used to model the effect of food group and item diversity during the first year of life on allergic outcomes up to 15 years. The regression results are reported as odds ratios with corresponding 95% confidence intervals.

Main models were adjusted for time of follow-up (outcome-specific), sex (male vs female), study area (Munich vs Leipzig vs Bad Honnef vs Wesel), family history of allergic diseases (yes vs no), breastfeeding during the first four months (yes vs in part vs no) and parental education (based on the highest number of years of school education of either parent: <10 years vs =10 years vs >10 years, according to the German educational system).

Several sensitivity analyses were conducted. First, models were additionally adjusted for early skin symptoms (total population only). Second, main models were additionally adjusted for birth weight (grams), presence of older siblings (yes vs no), maternal smoking during pregnancy (yes vs no) and tobacco smoke exposure in the home (yes vs no, ever from birth to 4 years) as a combined variable. Third, participants with partially missing outcome data (i.e. not available at all time points) were excluded from the analyses. Forth, children with any

missing data in original exposure variables were excluded from the analyses. Finally, effect modification by age was tested by introducing to the models an interaction term between exposure variable and outcome-specific time of follow-up.

All aforementioned analyses were conducted for entire study population as well as stratified by whether a child had early skin symptoms at the first year of life. This was done, as we previously found evidence for reverse causality between early skin symptoms and introduction of solids.¹

Data management was conducted using the program SAS, version 9.2 (SAS Institute Inc., Cary, NC; USA). Statistical analyses were conducted using the program R, version 3.2.4 (Vienna, Austria).⁴ GEE models were fitted by the *geeglm* function from the *geepack* package.⁵ Running the analyses was simplified by using the *manyregs* package.⁶ Statistical significance level was considered at $p < 0.05$.

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Table S1. Description of the study population.

Characteristic	Complete study population (n=2518)	Participants without early skin symptoms during the first year (n=1011)	Participants with early skin symptoms during the first year (n=1507)	p-value ^s
Male sex	51.9	51.6	52.0	0.847
Centre				0.006
Munich	51.0	50.5	51.2	
Leipzig	28.6	26.0	30.4	
Bad Honnef	10.2	11.2	9.5	
Wesel	10.2	12.3	8.9	
Family history of allergic diseases - yes	57.2	51.1	61.3	<.0001
Breastfeeding during the first 4 months				0.612
exclusive	58.2	57.9	58.4	
partial	35.8	35.6	36.0	
no	6.0	6.5	5.6	
Parental education				0.005
low	4.3	5.9	3.3	
medium	26.8	27.6	26.2	
high	68.9	66.6	70.5	
Birth weight (grams)*	3475.8±440.7	3456.2±443.1	3488.9±438.7	0.124
Exposure to tobacco smoke in utero and at home between 0 and 4 years				0.003
definitely never	53.9	51.9	55.2	
likely never**	7.6	6.0	8.6	
in utero or at home ever	38.6	42.0	36.2	
Presence of older siblings – yes	43.7	46.3	42.0	0.035
Food group diversity during the first year				<.0001
0 – 5	19.9	15.6	22.8	
6	22.4	23.0	22.1	
7	29.3	31.6	27.7	
8	28.4	29.8	27.4	
Food item diversity during				0.034

the first year				
0 – 26	26.8	24.2	28.5	
27 – 30	23.3	23.4	23.2	
31 – 34	22.9	25.4	21.2	
35 – 48	27.0	26.9	27.1	
Eczema ever 2-15 years***	22.5	11.6	29.9	<.0001
Asthma ever 3-15 years***	6.9	4.6	8.3	0.001
Allergic rhinitis ever 3-15 years***	17.5	12.8	20.6	<.0001
Allergic sensitization to aeroallergens ever at 6, 10 or 15 years***	42.5	33.9	48.5	<.0001
Allergic sensitization to food allergens ever at 6, 10 or 15 years***	19.3	16.9	21.0	0.049

* Mean±Standard deviation

** Same as “definitely never” but data are partially missing.

*** There are some missing data due to different study population sizes depending on the outcome.

[§] Chi-Square test or two-tailed Mann–Whitney U test (for birth weight).

Table S2. Adjusted odds ratios with 95% confidence intervals of **diversity of food items during the first 1 year** and a range of allergic outcomes up to 15 years of life estimated by generalized estimating equations models. All models are adjusted for time of follow-up, sex, study area, family history of allergic diseases, breastfeeding during the first four months and parental education.

	Total study population	Participants without early skin symptoms	Participants with early skin symptoms
Eczema (2-15 years)			
Diversity of food items, quartiles			
0-26	1	1	1
27-30	0.84 (0.62-1.15)	1.29 (0.67-2.46)	0.83 (0.58-1.18)
31-34	0.75 (0.54-1.04)	1.17 (0.61-2.25)	0.78 (0.53-1.13)
35-48	0.86 (0.63-1.16)	1.01 (0.52-1.95)	0.88 (0.62-1.24)
Diversity of food items, continuous [§]	0.99 (0.97-1.01)	1.00 (0.97-1.03)	0.99 (0.97-1.01)
Asthma (3-15 years)			
Diversity of food items, quartiles			
0-26	1	1	1
27-30	0.96 (0.50-1.83)	0.98 (0.27-3.54)	0.95 (0.45-2.00)
31-34	1.33 (0.73-2.41)	0.54 (0.13-2.19)	1.74 (0.90-3.39)
35-48	0.91 (0.50-1.67)	0.80 (0.24-2.72)	0.98 (0.49-1.95)
Diversity of food items, continuous [§]	1.00 (0.97-1.03)	0.99 (0.93-1.04)	1.00 (0.97-1.04)
Allergic rhinitis (3-15 years)			
Diversity of food items, quartiles			
0-26	1	1	1
27-30	0.98 (0.67-1.43)	1.43 (0.67-3.05)	0.87 (0.56-1.35)
31-34	1.14 (0.79-1.64)	2.12 (1.04-4.29)²	0.94 (0.61-1.44)
35-48	0.96 (0.66-1.40)	1.56 (0.75-3.27)	0.81 (0.53-1.25)
Diversity of food items, continuous	0.99 (0.97-1.01)	1.02 (0.98-1.05)	0.98 (0.96-1.01)
Allergic sensitization to aeroallergens (at 6, 10 and 15 years)			
Diversity of food items, quartiles			

0-26	1	1	1
27-30	0.83 (0.60-1.13)	0.81 (0.43-1.55)	0.79 (0.54-1.16)
31-34	1.00 (0.73-1.38)	1.29 (0.72-2.31)	0.92 (0.62-1.37)
35-48	0.72 (0.52-0.98)¹	0.93 (0.51-1.69)	0.64 (0.44-0.94)²
Diversity of food items, continuous [§]	0.99 (0.97-1.00)	1.00 (0.97-1.03)	0.98 (0.96-1.00)
Allergic sensitization to food allergens (at 6, 10 and 15 years)			
Diversity of food items, quartiles			
0-26	1	1	1
27-30	0.79 (0.54-1.17)	0.71 (0.34-1.48)	0.87 (0.55-1.40)
31-34	1.19 (0.82-1.73)	1.06 (0.55-2.06)	1.36 (0.86-2.15)
35-48	0.92 (0.63-1.33)	1.09 (0.57-2.08)	0.85 (0.54-1.35)
Diversity of food items, continuous [§]	1.01 (0.99-1.03)	1.02 (0.99-1.06)	1.00 (0.97-1.02)

Significant associations ($p < 0.05$) are written in bold font.

¹ identifies that an effect estimate remained statistically significant in 1 out of 4 sensitivity analyses (additionally adjusted for early skin symptoms (total population only), additionally adjusted for birth weight, presence of older siblings, maternal smoking during pregnancy and tobacco smoke exposure in the home, exclusion of participants with partially missing outcome data, exclusion of participants with partially missing exposure data data,), ² – in 2 out of 4 sensitivity analyses, ³ – in 3 out of 4 sensitivity analyses, ⁴ – in 4 out of 4 sensitivity analyses (total population only).

[§] Odds ratio scaled per interquartile range increase (9 items).



Figure S1. Flow chart of study participants.

Main confounders: sex, centre, family history of allergic diseases, breastfeeding during first 4 months and parental education.