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Inverse associations between food diversity in the second year of life and allergic diseases

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ABSTRACT

Background: The influence of diet in early childhood on later allergic diseases is currently a highly debated research topic. We and others have suggested that an increased diet diversity in the first year of life has a protective effect on the development of allergic diseases.
Objective: This follow-up study aimed to investigate associations between diet in the second year of life and later allergic diseases.
Methods: A total of 1014 children from rural areas in 5 European countries (the Protection against Allergy: Study in Rural Environments or PASTURE birth cohort) were included. Information on feeding practices in their second year of life and allergic diseases were collected up to age 6 years. Multivariate logistic regressions were performed with different models considering reverse causality, such as excluding children with a positive sensitization to egg and those with a positive sensitization to cow's milk at the age of 1 year.
Results: An increased food diversity score during the second year of life was negatively associated with the development of asthma. Consumption of dairy products and eggs in the second year of life found an inverse association with reported allergic outcomes. Consumption of butter was strongly associated with protection against asthma and food sensitization. Egg was inversely associated with atopic dermatitis (odds ratio [OR], 0.17; 95% confidence interval [CI], 0.04-0.77). Yogurt and cow's milk were inversely associated with food allergy (OR for yogurt, 0.05; 95% CI, 0.01-0.55; OR for cow's milk, 0.31; 95% CI, 0.11-0.89).
Conclusion: Increased food diversity in the second year of life is inversely associated with the development of asthma, and consumption of dairy products might have a protective effect on allergic diseases.

Introduction

It is well documented that environmental factors in early life play an important role in the development of allergy in childhood. However, contributing factors, such as nutrition, still require further understanding. As an international prospective long-term birth cohort, the

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Protection Against Allergy: Study in Rural Environments (PASTURE) study contributes to this goal.[1] The PASTURE study was designed to investigate rural factors associated with protection against allergies and to determine at which period in early life they may be most effective. A more diverse diet in the first year of life has already been found to be protective against allergies in European countries.[2-5]

Numerous prospective studies and reviews have found that, despite potential risks of bacterial infection, early introduction of unprocessed cow's milk has a preventive association with the development of allergic diseases.[6-10] However, none of these studies were randomized clinical trials. The protective effect of unprocessed farm milk intake on asthma at school age was suggested to be related to a higher intake of omega-3 polyunsaturated fatty acids.[11] With regard to other dairy products, consumption of cheese and yogurt in early life was reported to be protective against the development of allergic diseases.[4,5,12] Conversely, a French study found that butter intake was associated with an increased prevalence of asthma.[13]

In a discussion on the effect of diet on the development of allergic conditions, a pediatric review highlighted that a healthy diet rich in antioxidants and omega-3 fatty acids might reduce the occurrence of allergic diseases.[14] Furthermore, Grimshaw et al[15] reported that a dietary pattern with a high intake of fruits, vegetables, and homemade foods in the first year of life was associated with less food allergy at the age of 2 years. In a meta-analysis from 2017 on the effects of fruit and vegetable intake on the risk of developing asthma, wheezing, and immune responses, most of the evaluated studies confirmed a protective effect against asthma.[16]

The interaction between diet and the gut microbiome with its metabolites has been described as one underpinning mechanism mediating the protective effect of nutrition on allergic diseases. Among these metabolites are short-chain fatty acids (SCFAs), such as acetate, propionate, and butyrate, produced by the gut microbiome by fermentation of fiber. The SCFAs have broad anti-inflammatory effects, which are associated with protection against allergies and inflammatory bowel disease.[17,18]

We previously found a protective association between the intake of cow's milk products, especially yogurt, an increased food diversity within the first year of life and later allergic disease.[4,5] This present study aimed to follow-up these children and to document any association between diet in the second year of life and later allergic diseases up to the age of 6 years. Currently, dietary interventions for primary allergy prevention have focused on the first year of life. However, the introduction of solid foods to an infant's diet can be challenging for parents, especially when implementing the recommendation of a more diverse diet in early life. Therefore, nutrition in the second year of life might be of considerable interest as a continuous strategy for allergy prevention. To our knowledge, so far there have been no studies analyzing diet diversity beyond the first year of life, which makes this prospective study unique.

Methods

Study Design

As a prospective birth cohort study, the PASTURE study included 1133 children from rural areas in Austria, Finland, France, Germany, and Switzerland. Initially, between August 2002 and March 2005, pregnant women were recruited in their third trimester of pregnancy. Those living on a farm were allocated to the farm group, the rest was held as the reference group. In all 5 countries, the study went through the local ethics committee; written informed consent was gained from all parents. The detailed study design is available elsewhere.[1]

Study Population

A total of 1014 children of the PASTURE birth cohort with data available on allergic diseases up to age 6 years, nutrition within the second year of age, parental allergic history, number of siblings, pets, mode of delivery, pregnancy smoking status, and breastfeeding during the first year of life were included in these analyses.

Exposures Definition

Data on nutrition in the second year of life were collected in questionnaires at 1.5 and 2 years of age. The following food items were reported in those questionnaires and, therefore, included in our analyses: yogurt, butter (only butter, not margarine), cow's milk, cheese, egg, meat, fish, nuts, vegetables, fruits, and cereals. A food diversity score (FDS), which included these items, was calculated as the number of different food items included in the child's diet within the second year of life, resulting in a score from 0 to 11. The FDS item numbers differed between the first and second year (15 and 11 items, respectively), owing to differences in food items reported at these periods. For the categorization of the FDS, we performed latent class analysis. When doing latent class analysis, the best model was with 2 classes, less than or equal to 8 or greater than 8. Therefore, we decided to categorize the FDS with 1 class ($\leq$8) but still keeping 2 more categories for FDS greater than 8 (FDS 9-10 and FDS 11) to include more information.

Outcomes Definition

Atopic dermatitis (AD) and food allergy were defined as physician diagnoses reported in the year 4-, 5- and 6-year questionnaires. Children were defined as having asthma when parents reported that the child had either a physician diagnosis of asthma or at least 2 episodes of physician diagnosis of spastic, obstructive, or asthmatic bronchitis in the 4-, 5-, or 6-year questionnaire, independently of a history of asthma in the first 3 years.

Atopic sensitization at the age of 6 years was defined as the presence of specific immunoglobulin E (IgE) to foods (hen's egg, cow's milk, peanut, hazelnut, carrot, and wheat flour) or inhalants (*Dermatophagoides pteronyssinus, D. farinae*, alder, birch, hazel, grass pollen, rye, mugwort, plantain, cat, horse, dog, alternaria) with levels of at least 0.35 kU/L.

Statistical Analysis

Logistic regressions were performed to test for associations between food exposure and AD, food allergy, asthma, and atopic sensitization. Odds ratios (OR), adjusted for the following potential confounders: sex, center, farming status, parental allergic status, mode of delivery, number of siblings, smoking during pregnancy, contact with pets (cats and dogs) in the first year of life, breastfeeding, and FDS at 12 months, as previously described, were calculated.[5] Confounders were selected depending on their effect on the OR (change of >10%). However, some variables such as farmer, sex, breastfeeding are well known as potential confounders and were, therefore, still kept in the adjusted model. For all the analyses, we excluded children with a diagnosis of AD up to the age of 1 year (n = 147) and children with sensitization to egg and cow's milk at the age of 1 year (specific IgE $\geq$ 0.35 kU/L) (n = 60) to consider reverse causality. Those 2 allergens were chosen because they represent the 2 most frequent food allergies in early life; other sensitizations were much less prevalent and were, therefore, not considered for exclusion. Moreover, a sensitivity analysis in a subgroup of children with no specific exclusion of cow's milk products in the first year of life was performed.

Statistical analysis was performed using STATA (version 12.1; StataCorp LLC, College Station, Texas) and Statistical Analysis System software, version 9.4 (SAS Institute, Inc, Cary, North Carolina). Statistical significance was accepted at *P* less than.05.

Results

We included 1014 children (out of 1133 at baseline) in the analyses and divided them into subgroups according to their FDS within the second year of life (Table 1). Three food diversity patterns were selected: consumption of 8 or fewer food items, consumption of 9 to 10 items, and consumption of all 11 food items. Within these groups, sex, farmer status, having at least 1 sibling, exposure to pets, and smoking status in pregnancy were equally scattered. However, atopic parents were more frequent in the low food diversity group (FDS ≤ 8) and breastfeeding was least prevalent in this group. Differences between centers were observed, with French participants having the highest percentage of participants in the FDS ≤ 8. Correlation with the FDS from the first year of life revealed that infants who had been in the low and medium FDS mostly remained in the low FDS in the second year, but children from the 6 to 15 items score progressed into the higher FDS. The most discriminating differences between the 3 groups were seen in butter, egg, fish, nuts, cow's milk, cheese, and cereals consumption, whereas, the other items seemed to be consumed by the majority in the 3 groups.

The outcomes of AD, asthma, and food allergy were less prevalent in the medium and high FDS groups.

Food Diversity in the Second Year of Life and Allergic Diseases

Among children with no sensitization to cow's milk or egg and no AD in the first year of life, an inverse and linear relationship were observed between an increased diet diversity in the second year of life, as reflected by an increasing score (FDS as a continuous variable) and AD and asthma (Fig 1A-B). We found a significant reduction of 25% for the development of asthma with each additional food item introduced in the second year of life. This pattern was not observed for the relationship between FDS and food allergy (Fig 1C). Children with a low FDS in the second year of life (≤ 8 food items) had an increased risk of developing asthma, among children with no sensitization to cow's milk or egg at 1 year (Table 2). After excluding children with AD in the first year of life, an increased risk for asthma remained with a low food diversity, however, only a tendency was observed for AD. As 4 of the food items included in the FDS are dairy products, we calculated a FDS without dairy products (0 to 7). The analyses, again among children with no sensitization to cow's milk or egg and no AD in the first year of life, exhibited still a negative association between this new FDS (without dairy products) and AD and asthma (OR for AD, 0.70; 95% confidence interval [CI], 0.50-0.97 and after adjustment: 0.79; 95% CI, 0.54-1.14; for asthma: 0.74; 95% CI, 0.50-1.10, and after adjustment: 0.69; 95% CI, 0.45-1.08).

In addition, we combined the FDS in the first and second years of life in a new variable with 4 categories (children with a low or high FDS at 1 year and a low or high FDS at 2 years) (Table 3). For these analyses, only children with sensitization to egg or cow's milk at 1 year were excluded. Additional exclusion of children with AD in the first year enabled us to perform the analyses because of the small

Table 1
Patient Characteristics, Classified by Food Diversity Score Groups

Characteristic	Total		FDS in the second year of life						
			FDS ≤ 8		FDS 9-10		FDS 11		
Total	N = 1014	%	n = 73	%	n = 440	%	n = 329	%	*P* value
Sex: female	495/1012	48.9	32/73	43.8	218/440	49.6	162/328	49.4	.65
Farmer: yes	486/1014	47.9	33/73	45.2	226/440	51.4	178/329	54.1	.37
Atopic parents[a] (at least 1 parent)	536/1009	53.1	49/73	67.1	231/438	52.7	153/329	46.5	**.005**
Siblings: yes (at least 1)	641/1014	63.2	48/73	65.8	287/440	65.2	208/329	63.2	.93
C-section: yes	176/1005	17.5	12/72	16.7	71/436	16.3	58/326	17.8	.86
Pets (dogs and/or cats) in first year: yes	570/997	57.2	34/72	47.2	263/436	60.3	196/326	60.1	.10
Breastfeeding: yes	900/996	90.4	59/72	81.9	401/436	92.0	304/325	93.5	**<.001**
Center									**<.001**
Austria	206/1014	20.3	8/73	11.0	64/440	14.5	97/329	29.5	
Switzerland	213/1014	21.0	11/73	15.1	90/440	20.5	92/329	28.0	
France	187/1014	18.4	29/73	39.7	83/440	18.9	18/329	5.5	
Germany	231/1014	22.8	14/73	19.2	96/440	21.8	95/329	28.9	
Finland	177/1014	17.5	11/73	15.1	107/440	24.3	27/329	8.2	
Smoking pregnancy: yes	133/1014	13.1	8/73	11.0	60/440	13.6	33/329	10.0	.30
FDS in the first year of life									**.002**
0-1 items	18/995	1.8	2/72	2.8	7/433	1.6	3/325	0.9	
2-5 items	61/995	6.1	11/72	15.3	20/433	4.6	13/325	4.0	
6-15 items	916/995	92.1	59/72	81.9	406/433	93.8	309/325	95.1	
Food items									
Yogurt	998/1008	99.0	65/73	89.0	438/440	99.6	329/329	100.00	**<.001**
Butter	860/969	88.8	32/73	43.8	377/440	85.7	329/329	100.00	**<.001**
Egg	973/993	98.0	56/73	76.7	438/440	99.6	329/329	100.00	**<.001**
Meat	1010/1011	99.9	72/73	98.6	440/440	100.0	329/329	100.00	**.005**
Fish	919/1014	90.6	50/73	68.5	384/440	87.3	329/329	100.00	**<.001**
Nuts	515/897	57.4	7/73	9.6	150/440	34.1	329/329	100.00	**<.001**
Vegetables	1008/1013	99.5	69/73	94.5	439/440	99.8	329/329	100.00	**<.001**
Fruits	1012/1014	99.8	71/73	97.3	440/440	100.0	329/329	100.00	**<.001**
Cereals	913/984	92.8	48/73	65.8	405/440	92.1	329/329	100.00	**<.001**
Cow's milk	801/980	81.7	31/73	42.5	339/440	77.1	329/329	100.00	**<.001**
Cheese	918/1013	90.6	40/73	54.8	403/440	91.6	329/329	100.00	**<.001**
Reported allergic outcomes									
AD 3-6 y	133/853	15.6	18/58	31.0	52/382	13.6	31/278	11.2	**<.001**
Asthma 3-6 y	77/866	8.9	15/60	25.0	35/392	8.9	18/279	6.5	**<.001**
Food allergy 3-6 y	36/824	4.4	8/52	15.4	10/370	2.7	9/279	3.2	**<.001**
Food sensitization 6 y	280/724	38.7	17/44	38.6	137/338	40.5	90/226	39.8	.96
Inhalant sensitization 6 y	274/724	37.8	18/44	40.9	117/338	34.6	89/226	39.4	.44
Any sensitization 6 y	387/724	53.5	19/44	56.8	179/338	53.0	122/226	54.0	.88

Abbreviations: AD, atopic dermatitis; C-section, cesarean section; FDS, food diversity score.
NOTE. Boldface values are significant ($P < .05$).
[a]At least 1 parent (mother or father) with a history of asthma, hay fever, or AD.

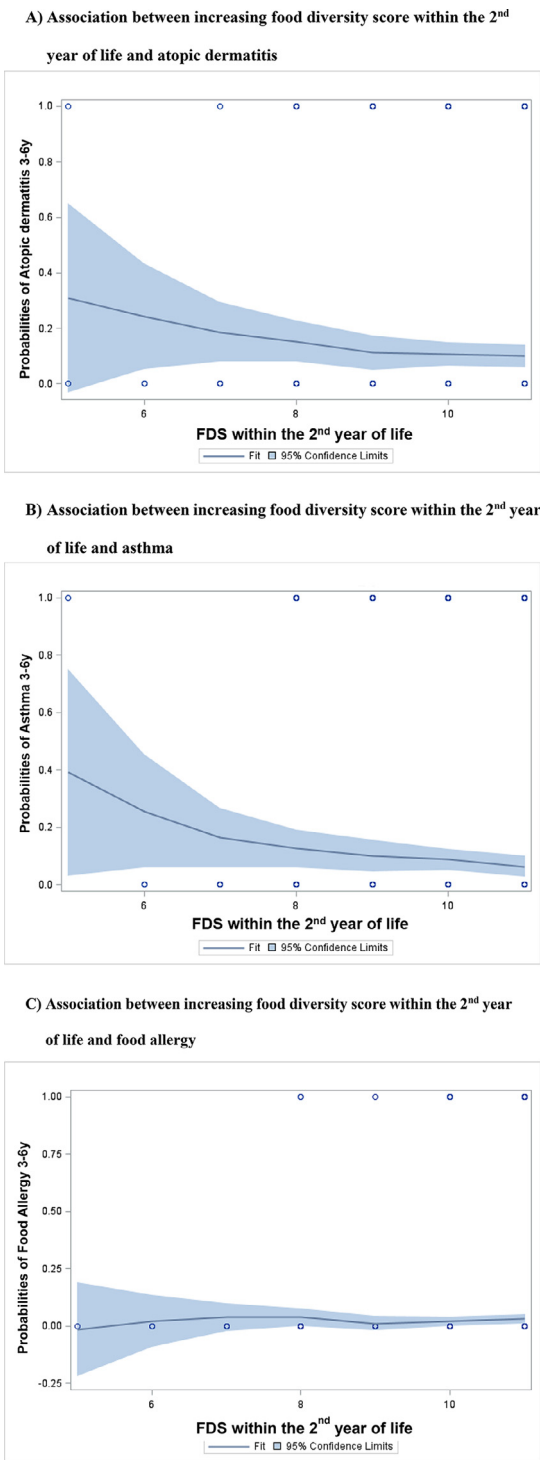

Figure 1. (A) Association between increasing food diversity score within the second year of life and AD. The solid line represents the predicted probabilities of AD as a function of the FDS. The OR for AD with each additional food item introduced in the second year of life was 0.84 (95% CI [0.66-1.07]). (B) The association between increasing FDS within the second year of life and asthma. The solid line represents the predicted probabilities of asthma as a function of the FDS. The OR for asthma with each additional food item introduced in the second year of life was 0.75 (95% CI [0.58-0.98]). (C) The association between increasing FDS within the second year of life and food allergy. The solid line represents the predicted probabilities of food allergy as a function of the FDS. The OR for food allergy with each additional food item introduced in the second year of life was 1.05 (95% CI [0.60-1.85]). The FDS include 11 food items, namely: yogurt, butter, cow's milk, cheese, egg, meat, fish, nuts, vegetables, fruits, and cereals. Children with positive IgE to cow's milk or to egg at the age of 1 year (≥ 0.35 kU/L) and children with AD in the first year of life were excluded. AD, atopic dermatitis; CI, confidence interval; FDS, food diversity score; IgE, immunoglobulin E; OR, odds ratio.

Table 2
Food Diversity in the Second Year of Life and Allergic Outcomes

Outcomes	Model 1: N	%	OR	95% CI		aOR[a]	95% CI		Model 2: N	%	OR	95% CI		aOR[a]	95% CI)		Model 3: N	%	OR	95% CI		aOR[a]	95% CI
AD 3-6 y																							
FDS category																							
- ≤ 8 items	15/51	29.4	**3.21**	**(1.57–6.54)**		2.05	(0.91–4.61)		8/41	19.5	2.24	(0.93–5.41)		1.69	(0.65–4.40)		7/36	19.4	2.17	(0.86–5.51)		1.57	(0.57–4.33)
- 9-10 items	51/365	14.0	1.25	(0.77 2.03)		1.04	(0.62–1.76)		34/328	10.4	1.07	(0.62–1.86)		0.90	(0.50–1.63)		34/312	10.9	1.10	(0.63–1.93)		0.88	(0.48–1.60)
- 11 ref	30/261	11.5	1			1.00			24/246	9.8	1.00			1.00			23/230	10.0	1.00			1.00	
FDS continuous			**0.77**	**(0.65–0.93)**		0.89	(0.73–1.09)				0.84	(0.67–1.06)		0.92	(0.71–1.19)				0.84	(0.66–1.07)		0.94	(0.72–1.22)
Asthma 3-6 y																							
FDS category																							
- ≤ 8 items	13/54	24.1	**4.57**	**(2.07–10.11)**		**3.37**	**(1.37–8.27)**		7/41	17.1	**3.10**	**(1.18–8.16)**		**3.27**	**(1.15–9.36)**		6/36	16.7	**3.02**	**(1.08–8.44)**		**3.01**	**(1.01–9.41)**
- 9-10 items	34/374	9.9	1.44	(0.79–2.64)		1.34	(0.70–2.54)		30/334	89.0	1.49	(0.78–2.83)		1.43	(0.71–2.86)		29/317	9.2	1.52	(0.78–2.94)		1.50	(0.74–3.04)
- 11 ref	17/262	6.5	1.00			1.00			15/241	6.2	1.00			1.00			14/225	6.2	1.00			1.00	
FDS continuous			**0.67**	**(0.54–0.83)**		**0.73**	**(0.57–0.92)**				**0.76**	**(0.59–0.97)**		**0.76**	**(0.57–0.99)**				**0.75**	**(0.58–0.98)**		0.76	(0.57–1.01)
Food allergy 3-6 y																							
FDS category																							
- ≤ 8 items	6/46	13.0	**4.22**	**(1.42–12.49)**		2.89	(0.84–9.96)		2/37	5.4	1.94	(0.39–9.73)		1.81	(0.30–10.9)		2/33	6.1	2.05	(0.40–10.30)		1.87	(0.30–11.66)
- 9-10 items	8/353	2.3	0.65	(0.25–1.71)		0.49	(0.18–1.38)		6/318	1.9	0.65	(0.22–1.92)		0.58	(0.17–1.92)		5/303	1.7	0.53	(0.17–1.70)		0.44	(0.12–1.56)
- 11 ref	9/262	3.4	1			1.00			7/245	2.9	1.00			1.00			7/229	3.1	1.00			1.00	
FDS continuous			**0.67**	**(0.50–0.90)**		0.75	(0.53–1.05)				1.05	(0.61–1.79)							1.05	(0.60–1.85)		1.20	(0.62–2.31)

Abbreviations: AD, atopic dermatitis; aOR, adjusted odds ratio; CI, confidence interval; FDS, food diversity score; IgE, immunoglobulin E; NA, not available; OR, odds ratio.
NOTE. The 11 food items include yogurt, butter, cow's milk, cheese, egg, meat, fish, nuts, vegetables, fruits, and cereals. Model 1: exclusion of children with positive IgE to cow's milk or to egg at the age of 1 year (≥ 0.35 kU/L); model 2: exclusion of children with AD in the first year of life; model 3: exclusion of children with both positive IgE to cow's milk or to egg at the age of 1 year (≥ 0.35 kU/L) and children with AD in the first year of life. Boldface values are significant ($P < .05$).
[a]Adjusted for sex, center, farmer status, atopic parents, contact to pets in the first year of life, breastfeeding, smoking during pregnancy, and FDS in the first year of life.

Table 3
Food Diversity Scores in the First and Second Year of Life Combined and Allergic Diseases

FDS score	N	%	OR	95% CI
AD 3-6 y				
FDS category				
- FDS 1 y low & FDS 2 y low	3/6	50.0	**6.82**	**(1.35-34.39)**
- FDS 1 y low & FDS 2 y high	3/21	14.3	1.14	(0.33-3.95)
- FDS 1 y high & FDS 2 y low	11/44	25.0	**2.27**	**(1.10-4.68)**
- FDS 1 y high & FDS 2 y high, ref	77/602	12.8	1.00	
Asthma 3-6 y				
FDS category				
- FDS 1 y low & FDS 2 y low	2/6	33.3	**6.00**	**(1.07-33.62)**
- FDS 1 y low & FDS 2 y high	3/21	14.3	2.00	(0.57-7.04)
- FDS 1 y high & FDS 2 y low	10/47	21.3	**3.24**	**(1.52-6.93)**
- FDS 1 y high & FDS 2 y high, ref	47/611	75.8	1.00	
Food allergy 3-6 y				
FDS category				
- FDS 1 y low & FDS 2 y low	2/4	50.0	**33.88**	**(4.50-255.02)**
- FDS 1 y low & FDS 2 y high	0/19	0	NA	
- FDS 1 y high & FDS 2 y low	4/41	9.8	**3.66**	**(1.17-11.44)**
- FDS 1 y high & FDS 2 y high, ref	17/593	2.9	1.00	

Abbreviations: AD, atopic dermatitis; CI, confidence interval; FDS, food diversity score; IgE, immunoglobulin E; OR, odds ratio.
NOTE. FDS at 1 and 2 years of age combined (FDS 1 year low = ≤ 3 food items, FDS 1 year high = > 3 food items; FDS 2 year low = ≤ 8, FDS 2 year high = > 8). Children with positive IgE to cow's milk or to egg at the age of 1 year (≥ 0.35 kU/L) were excluded. Boldface values are significant ($P < .05$).

numbers. The strongest positive association with AD, asthma, and food allergy was observed in children with low FDS at both time points. Nevertheless, a low FDS in the second year of life was positively associated with allergic diseases, independently of the FDS in the first year.

Single Food Items in the Second Year of Life and Allergic Diseases

The subsequent analyses were performed excluding children with AD within the first year of life and excluding children with sensitization to egg or cow's milk (IgE ≥ 0.35 kU/L). A negative association between egg and cereals consumption in the second year of life and AD was observed (Fig 2A). Butter exhibited a tendency toward a negative association with AD.

Regarding asthma, we found an inverse association between butter toward asthma (OR, 0.42; 95% CI, 0.20-0.86) (Fig 2B). Nuts and cow's milk exhibited protective tendencies.

Yogurt and cow's milk were inversely associated with food allergy (OR for yogurt, 0.05; 95% CI, 0.01-0.55; OR for cow's milk, 0.31; 95% CI, 0.11-0.89) (Fig 2C). Concerning food sensitization, butter was protectively associated, nuts exhibited a protective tendency, and cow's milk and cereals were positively associated (Fig 2D).

Analyses Among Children With no Exclusion of Cow's Milk Products in the First Year of Life

Cow's milk allergy is the most frequent food allergy in early life and is associated with other allergic diseases. Therefore, we performed analyses in a subgroup of children for whom no specific exclusion of cow's milk was reported in the first year of life. This subgroup encompassed a total of 885 children (78%) and was done to reduce the potential effect of reverse causation. The calculated adjusted OR exhibited an inverse association between egg and AD (Table 4). Moreover, egg seemed to have a protective tendency against food sensitization; however, numbers were small. Yogurt consumed in the second year of life was negatively associated with food allergy. Butter exhibited an evident protective association with food sensitization (adjusted OR, 0.51; 95% CI, 0.28-0.92). No associations were observed with the outcome of asthma.

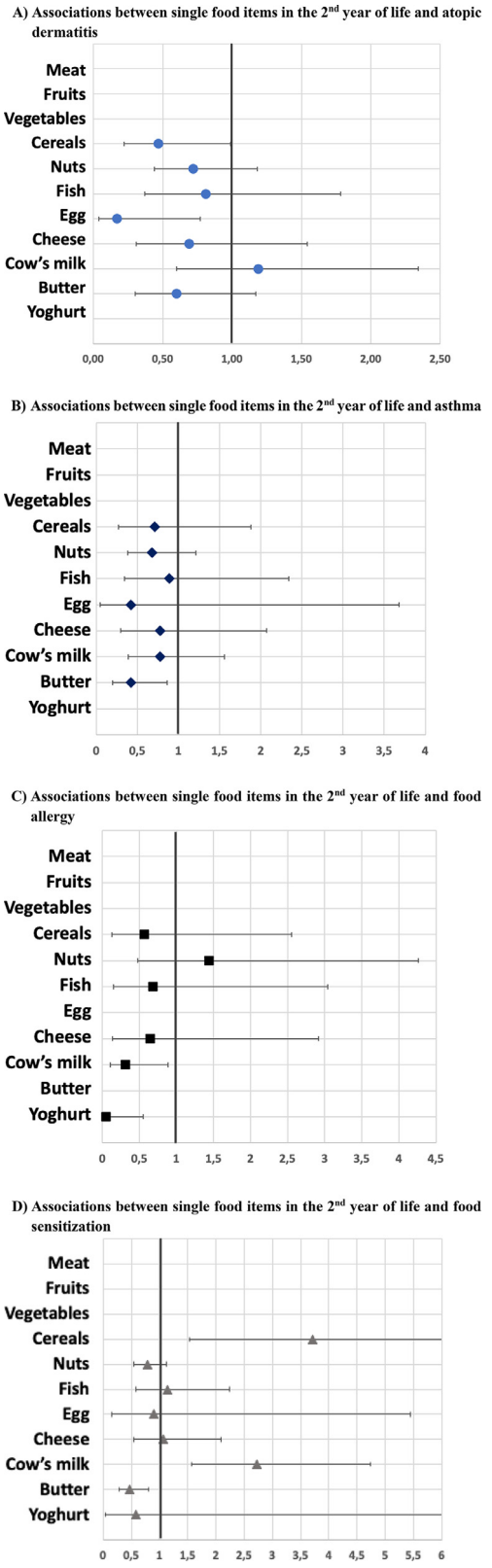

Figure 2. (A) Associations between single food items in the second year of life and AD. (B) Associations between single food items in the second year of life and asthma. (C) Associations between single food items in the second year of life and food allergy. (D) Associations between single food items in the second year of life and food sensitization. Odds ratios and 95% CI for health outcomes (from 3-6 years of age) with different food items consumed within the second year of life are illustrated. For some food items, there are no applicable results because of small numbers. Children with both positive IgE to cow's milk or to egg at the age of 1 year (≥ 0.35 kU/l) and children with AD in the first year of life were excluded. AD, atopic dermatitis; CI, confidence interval; IgE, immunoglobulin E.

Table 4
Associations Between Food Items and Allergic Diseases Among Children With No Exclusion of Cow's Milk Products in the First Year of Life

Food items	N	AD aOR 95% CI	N	Asthma aOR 95% CI	N	Food allergy aOR 95% CI	N	Food sensitization aOR 95% CI
Yogurt								
yes	106/652	0.53 (0.05-5.94)	53/657	NA	16/626	**0.04 (0.002-0.72)**	215/557	NA
no	1/4	1	0/3	—	1/3	1	2/2	—
Butter								
yes	83/546	0.99 (0.52-1.89)	45/552	0.62 (0.26-1.50)	16/534	2.44 (0.30-20.16)	166/456	**0.51 (0.28-0.92)**
no	18/82	1	8/80	1	1/72	1	40/75	1
Cow's milk								
yes	81/531	1.27 (0.59-2.74)	42/533	1.34 (0.54-3.35)	12/512	0.47 (0.10-2.23)	196/450	1.81 (0.94-3.51)
no	18/99	1	9/102	1	4/94	1	19/84	1
Cheese								
yes	96/603	0.73 (0.33-1.63)	47/607	0.94 (0.34-2.59)	15/578	1.11 (0.13-9.43)	199/517	0.71 (0.35-1.42)
no	10/54	1	6/54	1	2/52	1	19/44	1
Egg								
yes	99/636	**0.20 (0.05-0.88)**	50/638	0.40 (0.07-2.17)	16/611	0.30 (0.03-3.29)	210/539	0.31 (0.08-1.25)
no	6/10	1	2/11	1	1/8	1	6/11	1
Fish								
yes	102/610	1.13 (0.41-3.09)	48/613	0.83 (0.26-2.62)	15/584	0.48 (0.09-2.45)	206/524	1.75 (0.78-3.89)
no	5/48	1	5/49	1	2/47	1	12/37	1
Nuts								
yes	39/312	0.91 (0.52-1.59)	23/316	0.64 (0.31-1.31)	8/308	1.004 (0.30-3.34)	102/264	0.88 (0.55-1.41)
no	53/275	1	26/275	1	7/259	1	95/242	1
Cereals								
yes	90/588	1.03 (0.47-2.23)	47/591	0.94 (0.28-3.17)	15/566	0.32 (0.05-2.04)	202/498	1.15 (0.51-2.61)
no	13/55	1	5/55	1	2/51	1	10/51	1
Vegetables								
yes	106/655	0.27 (0.02-4.87)	52/658	0.15 (0.01-1.97)	17/627	NA	217/558	NA
no	1/2	1	1/3	1	0/3	—	0/2	—
Fruits								
yes	107/658	NA	53/662	NA	17/631	NA	218/561	NA
no	0	—	0	—	0	—	0	—
Meat								
yes	107/655	NA	53/660	NA	17/629	NA	216/558	NA
no	0/1	—	0	—	0/1	—	1/1	—

Abbreviations: AD, atopic dermatitis; aOR, adjusted odds ratio; CI, confidence interval; FDS, food diversity score; IgE, immunoglobulin E; NA, not available; OR, odds ratio.
NOTE. Adjusted OR for sex, center, farmer, parental allergic status, contact to pets in the first year of life, mode of delivery, breastfeeding, siblings, smoking in pregnancy, and FDS at 12 months of age. Boldface values are significant ($P < .05$).

Discussion

In this study, we found that an increased food diversity during the second year of life is negatively associated with the development of asthma, suggesting a protective effect. In addition, a trend for a negative association between an increasing food diversity during the second year of life and AD was observed. Second, our findings highlight the fact that dairy products and eggs consumed within the second year of life might have preventive effects against the development of allergic diseases by 6 years of age.

Our results are in line with previous studies, which reported that consumption of dairy products in early life has a protective association with the development of allergies.[6,7,8,10,12] A discrepancy between the effect of cow's milk on food allergy (negative association) and food sensitization (positive association) was found, which might be owing to a high sensitization rate without clinically evident food allergy. Allergen sensitization itself is a complex host-immune factor interaction and sensitization alone does not implicate allergy.[19] Moreover, in the Learning Early About Peanut Allergy or LEAP study, it was found that an early peanut introduction led to better peanut allergy prevention than avoidance, and this was also among sensitized children.[20] To date, most of the studies have investigated the benefits of unprocessed cow's milk. Here, we propose that dairy products, in general, have a beneficial correlation with allergic diseases. Further investigation in relation to processing methods and their impact on milk components will be needed. As early as 2003, Wijga et al[21] stated that asthma was less prevalent in 3-year-old children receiving full cream milk and butter daily. A previous Finnish longitudinal study that analyzing food habits in children aged 3 to 18 years reported that atopic children consumed more margarine than nonatopic patients.[22] Our overall cheese item exhibited an inverse tendency with AD and asthma, thus, supporting the results of Nicklaus et al[12] who, among PASTURE children, found negative associations between cheese consumption from 12 to 18 months and AD and food allergy. In addition, results from the PASTURE group revealed that raw farm milk consumption was associated with an increased expression of innate immunity receptors at 1 year of age.[23]

Our results are consistent with the continued beneficial effect of increased diet diversity on allergic diseases, as we previously found for the first year of life.[5] After adjustment with the FDS from the first year of life and combined analysis of FDS at 1 and 2 years of age, we can state that an increased diet diversity in the second year of life might be considered as an independent protective factor on the development of allergic diseases, especially on asthma.

A limitation of this study consists of the selected rural study population. It, thus, remains unclear if these results can be extrapolated to urban children because allergies are proven to be a multifactorial disease. The strengths of the study are the prospective and international study design, the detailed data on nutrition, and an accurate follow-up. Although reverse causality cannot be completely excluded, this potential bias, present in all analyses of associations between diet and allergic diseases, was minimized by excluding children with egg or cow's milk sensitization and those having AD at age 1 year. We also performed additional analyses excluding children with specific food exclusions. By performing the analyses in those subgroups of children, we better take into account the reverse causality, but it results in a loss of statistical power.

In terms of the links between the gut microbiome, SCFA, and allergy, Arrieta et al,[24] analyzing participants of the Canadian Healthy Infant Longitudinal Development cohort in Canada, have identified harmful gut microbiota by deciphering microbes who were present in children at risk for asthma, showing a gut dysbiosis in their first 100 days of life. Von Mutius[25] highlighted the strengths of the microbiome as a counteractor of asthma as illustrated by farm and Amish children. Our results from PASTURE data illustrated that high levels of SCFAs in feces of children at 1 year were associated with less atopic sensitization.[17] Interestingly, this is the same population that we included in this study and results are consistent, in the sense that dairy products, which contain SCFAs, especially butyrate, have a protective effect against allergy. Moreover, we recently found that diverse feeding patterns and consumption of cow's milk and egg directly from a farm are related to the maturation of the gut microbiome.[26] In a more international comparison, de Filippo et al[27] revealed noteworthy differences in the gut microbiota of Italian and African children. A clearly higher amount of SCFAs was found in the African cohort, whose diet was low in fat and animal protein but rich in fiber. The SCFAs derived from skimmed milk has been found to have regulatory effects on cytokines and of being anti-inflammatory.[28] Moreover, in a mouse model, high fiber feeding was found to be protective against food allergies.[29] Hence, the books are still open over SCFAs and their potential for modifying multiple diseases through regulation of host metabolism, cell proliferation, and the immune system.[30,31]

In conclusion, our results from this cohort study reveal inverse associations between an increased food diversity in the second year of life and asthma. In addition, dairy product consumption in the second year of life was associated with a reduced risk of allergic diseases. However, to completely exclude reverse causality, randomized clinical trials need to be conducted. This study emphasizes the potential protective association of diet diversity against asthma and likely against other allergic diseases beyond the first year of life. As the first year of life holds challenges with diverse food introduction, the second year of life might still be a window of opportunity concerning diet diversity or diet recommendations for allergy prevention. We would like to underscore the importance of a continuous feeding practice of all types of food even in atopic families.

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