Food diversity in infancy and the risk of childhood asthma and allergies

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Background: Recently, the bacterial diversity of the intestinal flora and the diversity of various environmental factors during infancy have been linked to the development of allergies in childhood. Food is an important environmental exposure, but the role of food diversity in the development of asthma and allergies in childhood is poorly defined.

Objective: We studied the associations between food diversity during the first year of life and the development of asthma and allergies by age 5 years.

Methods: In a Finnish birth cohort we analyzed data on 3142 consecutively born children. We studied food diversity at 3, 4, 6, and 12 months of age. Asthma, wheeze, atopic eczema, and allergic rhinitis were measured by using the International Study of Asthma and Allergies in Childhood questionnaire at age 5 years.

Results: By 3 and 4 months of age, food diversity was not associated with any of the allergic end points. By 6 months of age, less food diversity was associated with increased risk of allergic rhinitis but not with the other end points. By 12 months of age, less food diversity was associated with increased risk of any asthma, atopic asthma, wheeze, and allergic rhinitis.

Conclusion: Less food diversity during the first year of life might increase the risk of asthma and allergies in childhood. The mechanisms for this association are unclear, but increased dietary antigen exposure might contribute to this link.

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Key words: *Asthma, allergic rhinitis, atopic eczema, wheeze, food diversity, children*

The disease process leading to asthma and allergies is initiated very early in life, probably before birth.[1-3] These early stages of life are most critical for the development of these diseases because of the key maturation processes the immune system is undergoing.[1-4] Encounters of the immune system with certain environmental antigens during these periods might intervene with the maturation processes.[2-5] This can lead to inappropriate immune responses and subsequent increased susceptibility to allergies and other immune-mediated ailments.[2-5]

The gut flora primarily drives the postnatal maturation of the immune system and the induction of a balanced immunity.[5-8] Postnatal commensal microbial exposures are required for appropriate immune tolerance and for maintaining adequate immunomodulatory capacity.[5,8,9] Recent studies show that a reduced bacterial diversity of the infant's intestinal flora increases the risk of atopic sensitization during childhood.[10-12] Low environmental biodiversity, characterized by the vegetation cover of the yards and land use around the homes, is also associated with low composition of classes of bacterial flora on the skin, as well as the development of atopic sensitization.[13]

Prenatal and infant feeding is a key environmental exposure that plays a fundamental role in the maturation process of the immune system and in shaping the composition of the gut microbiota, with the first encounter during infancy being human milk.[6,14] Early-life dietary exposures are key stimulants of the immunomodulatory circuits that could trigger atopic sensitization.[2,4-6,15,16] Maternal avoidance of suspected allergenic foods during pregnancy and lactation and delayed introduction of solid foods to the infant for the first 4 to 6 months have been perceived as primary prevention strategies for the development of allergies in childhood.[17-20] However, these strategies have not been effective thus far, and the recommendation on maternal dietary avoidance is now subject to change.[4,15] In contrast, recent evidence indicates that early introduction of complementary foods seems beneficial.[21-34]

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Abbreviations used
DIPP: Type 1 Diabetes Prediction and Prevention
ISAAC: International Study of Asthma and Allergies in Childhood

Although evidence is accumulating on the effect of the timing of introduction of new foods in the development of allergies in childhood, because of the limited number of studies, it is yet unclear whether the diversity of foods infants encounter during their first year of life might play any role in the development of childhood allergic ailments. Thus far, only 2 studies have investigated the role of food diversity during infancy in the development of allergies.[22,23,35] In the first study high food diversity was associated with an increased risk of atopic dermatitis at 2 years[22] but not at 6 years[23] of age. High food diversity during the first 12 months of life was associated with a decreased risk of atopic dermatitis at age 4 years in another study.[35]

We set out to study the association between food diversity during the first year of life and the development of asthma and allergies in childhood. On the basis of the current study population, we had separately showed that less food diversity as early as 3 months of age was associated with increased risk of sensitization to specific food and inhalant allergens at 5 years of age.[34] In the current article we report the results for clinical allergic outcomes: asthma and its phenotypes, wheeze, atopic eczema, and allergic rhinitis.

METHODS

Subjects and study design

We studied children participating in the Finnish Type 1 Diabetes Prediction and Prevention (DIPP) study, a multidisciplinary population-based prospective cohort study, which started in 1994.[36] Infants born with HLA-conferred susceptibility to type 1 diabetes were recruited from 3 university hospitals in Finland (Turku, Oulu, and Tampere) and monitored at 3- to 12-month intervals for diabetes-associated autoantibodies, growth, and environmental exposures. The study procedures were approved by local ethics committees, and parents signed a written informed consent form. A nutrition study was started within the DIPP study in Oulu and Tampere in September 1996 and October 1997, respectively. It examines the role of diet during pregnancy, lactation, infancy, and childhood in the development of type 1 diabetes and atopic diseases in childhood.[37] At the age of 5 years, 4075 children who were still participating in the dietary follow-up (born between September 2, 1996, and September 5, 2004) were invited to take part in the allergy study. Of these, 3781 (93% of those invited) took part, but only 3142 returned the International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire used for assessment of allergy symptoms.

Dietary assessment

The child's diet was assessed by using age-specific dietary questionnaires at ages 3, 6, and 12 months and a follow-up "age at introduction of new foods" form for recording the age at introduction of complementary foods. The questionnaires assessed the child's diet from birth until age 12 months and asked about breast-feeding; about use of infant formulas, cow's milk, and dietary supplements; and about the complementary foods the child had received. The questionnaires were returned to the study center at each age after completion. The "age at introduction of new foods" form was sent by mail to the families before the 3-month study center visit and kept until 2 years of age but checked by a trained study nurse at every clinic visit. The source of the complementary foods (whether prepared at home or purchased) the child has received was not differentiated by the questionnaire. The food exposures used for the calculation of food diversity were as follows: cow's milk and formula (as a combined variable); potatoes; carrots; turnip; fruits and berries (as a combined variable); cereals (rye, wheat, oats, and barley as a combined variable); other cereals (maize, rice, millet, and buckwheat as a combined variable), meat; fish; egg; cabbage; spinach; and lettuce. The correlation between most of these foods was minimal (range, 0.06-0.47), except for the correlation between each of potatoes, carrots, and fruits, which were between 0.70 and 0.88.

End point assessments

Families of the participating children completed a questionnaire modified from the ISAAC questionnaire on the child's history of allergic symptoms and asthma when the children were 5 years of age.[38,39] The asthma component of the questionnaire has been validated, resulting in excellent validity estimates.[40] A blood sample was also obtained from each child for the analysis of serum IgE, by which we were able to study both atopic and nonatopic asthma phenotypes by stratifying the results by atopy, as recently recommended.[41] We defined wheeze as having any of the following symptoms during the past 12 months: "wheezy sound in respiration," "wheezy sound in respiration in connection with physical activity," "difficulties in respiration in the morning on waking up," "wheezy respiration without having the sniffles or respiratory infection," or "dry cough at nights not associated with common colds or respiratory infections." We defined asthma as doctor-diagnosed asthma plus either any wheezing symptom or use of asthma medication during the past 12 months. Age at asthma diagnosis was determined by using the following question: "At what age was asthma diagnosed?" Allergic rhinitis was defined as sneezing, nasal congestion, or rhinitis other than with respiratory tract infections accompanied by itching of the eye and tearing during the past 12 months. Atopic eczema was defined as atopic eczema ever diagnosed by a doctor.

Sociodemographic and perinatal characteristics

Information on the child's sex, maternal age, maternal education, and number of siblings was recorded in a structured questionnaire completed by the parents after delivery. Information on the duration of gestation, mode of delivery, birth weight and length, and maternal smoking during pregnancy was retrieved from the Medical Birth Registries of Oulu and Tampere University Hospitals.

Statistical analysis

The Pearson χ^2 test was used to examine the relation of the background characteristics to food diversity at 3, 4, 6, and 12 months of age. We applied Cox regression to investigate the associations between food diversity and the risk of asthma. The proportionality of the hazards was tested by adding linear interaction terms of food diversity with time to the models. Logistic regression was used to investigate the associations between food diversity and the risk of atopic eczema, wheeze, and allergic rhinitis.

We defined food diversity as the number of complementary foods introduced at 3, 4, 6, and 12 months of age. Preferably 4 categories of food diversity at each time point were defined based on the distribution of the data at each time point: at 3 months, these were "no food item," "1-2 food items," and ">2 food items"; at 4 months, these were "no food item," "1-2 food items," "3-4 food items," and ">4 food items"; at 6 months, these were "0-4 food items," "5-6 food items," "7-8 food items," and ">8 food items"; and at 12 months, these were "0-7 food items," "8-9 food items," "10-11 food items," and ">11 food items."

In the Cox models dependence among siblings (there were 452 sibling pairs in the birth cohort) was taken into account by performing a marginal analysis with a working independence assumption and a robust sandwich estimator of variance. In the logistic regression models sibling dependence was taken into account by using the generalized estimating equations framework with the sandwich estimator of variance. Children whose respective end points had occurred before the time of each food exposure (3, 4, 6, and 12 months) were excluded from the analyses. As recently suggested,[42] the adjusted models

TABLE I. Number and percentage of children who were introduced to complementary foods by each time point during the first year of life

Complementary food	Frequency*	No. (%) of children introduced to foods, 0-3 mo	No. (%) of children introduced to foods, >3-4 mo	No. (%) of children introduced to foods, >4-6 mo	No. (%) of children introduced to foods, >6-12 mo
Cow's milk	3098	1956 (63)	264 (9)	554 (18)	312 (10)
Roots (potatoes, carrot, turnip)	3074	949 (31)	1493 (48)	610 (20)	22 (1)
Fruits and berries	3071	702 (23)	1351 (44)	961 (31)	57 (2)
Oats	2889	31 (1)	156 (5)	2326 (81)	340 (12)
Wheat	2861	21 (1)	104 (4)	1734 (60)	945 (33)
Rye	2815	11 (0.4)	73 (3)	1421 (50)	1246 (44)
Barley	2773	18 (1)	78 (3)	1359 (49)	1186 (43)
Wheat, rye, oats, barley	3053	42 (1)	196 (6)	2466 (81)	322 (11)
Other cereals (maize, rice, millet, buckwheat)	3036	269 (9)	680 (22)	1549 (51)	503 (17)
Meat	3045	5 (0.2)	87 (3)	2575 (85)	371 (12)
Fish	2919	1 (0)	21 (1)	1074 (37)	1581 (54)
Egg	2862	6 (0.2)	2 (0)	399 (14)	2098 (73)

*Number of children with available data for each food.

included the following potential confounding factors selected on a conceptual basis: sex of the child, number of siblings, parental asthma, parental rhinitis, delivery hospital, and maternal smoking during pregnancy. Other factors were selected based on statistical tests: season of birth, duration of gestation, maternal age, maternal basic education, pets at home by 1 year, mode of delivery, and birth weight.

We evaluated reverse causality by performing appropriate interaction tests between food diversity and eczema by 3 months (food diversity at 3 months), 4 months (food diversity at 4 months), 6 months (food diversity at 6 months), and 12 months (food diversity at 12 months) and parental allergy history in relation to the end points. If the interaction was significant ($P < .20$), the results were stratified by the corresponding term. We also performed interaction tests between food diversity and the duration of total breast-feeding and food allergy to determine whether breast-feeding and food allergy modified the associations between the food diversity and the end points. Statistical significance was taken as a 2-sided P value of less than .05. Multiplicity issues were taken into account in cautious interpretation of the results. SAS software (version 9.2; SAS Institute, Cary, NC) was used in the analyses.

RESULTS

Characteristics of the study population

Table I shows the proportion of children who were introduced to each complementary food at specific time points during the first year of life. The majority of children were introduced to cow's milk at between 0 and 3 months of age. More children received roots and fruits and berries between 3 and 4 months of age than in other periods. A majority of the infants received cereals (oats, wheat, rye, barley, and other cereals) and meat between 4 and 6 months of age, whereas most children received fish and egg between 6 and 12 months of age.

Table II shows the relation of the subjects' background characteristics to introduction of 2 or more food items at 3 months, 4 or more food items at 4 months, 8 or more food items at 6 months, and 11 or more food items at 12 months of age. Boys, children born in the region of Oulu (part of northern Finland), and children of mothers with less than a high school education were slightly more likely to have more diverse foods at 3 and 4 months of age but not later. Children with fewer numbers of siblings, those whose mothers smoked during pregnancy, those whose mothers were younger, and those who had pets at home during the first year of life were more likely to have more diverse foods at 3, 4, 6, and 12 months of age. Children whose parents had no history of asthma and those with longer duration of gestation were more likely to have more diverse foods at 12 months of age. Children delivered through cesarean section were more likely to have more diverse foods at 4 months of age.

Associations between food diversity and asthma and allergic symptoms

Table III shows the unadjusted and adjusted associations between food diversity during the first year of life and the incidence of asthma, whereas Table IV shows the associations for wheeze, atopic eczema, and allergic rhinitis. Clearly, food diversity at 3 and 4 months of age was not associated with any of the end points. At 6 months of age, less diversity of foods was associated with an increased risk of allergic rhinitis (Table IV). At 12 months of age, less diversity of foods was associated with increased risk of asthma and its phenotypes (Table III), wheeze, and allergic rhinitis (Table IV).

Interaction and stratified analyses by child's allergy history

We did not observe significant interactions between food diversity and food allergy and duration of breast-feeding in relation to any of the end points. However, we observed some significant interactions between food diversity and atopic eczema during year 1 and parental allergy in relation to the end points. These results were then stratified by these factors. The stratified results by the presence of eczema (see Table E1 in this article's Online Repository at www.jacionline.org) show that at 4 months of age, less food diversity was inversely associated with the risk of nonatopic asthma among children with no manifestation of atopic eczema by 4 months of age. At 6 and 12 months of age, less food diversity was associated with an increased risk of any asthma, atopic asthma, and allergic rhinitis among children with manifestations of atopic eczema by 6 and 12 months of age. Less food diversity at 12 months of age was associated with an increased risk of nonatopic asthma among children with no manifestation of atopic eczema by 12 months of age. The stratified results by parental allergy (see Tables E2 and E3 in this article's Online Repository at www.jacionline.org) show

TABLE II. Relation of the background characteristics of the study population to food diversity (number of foods introduced) at 3, 4, 6, and 12 months of age

		Food diversity at 3, 4, 6, and 12 mo							
	Frequency (n = 3142),	≥2 food items at 3 mo (n = 1338)		≥4 food items at 4 mo (n = 2199)		≥8 food items at 6 mo (n = 2385)		≥11 food items at 12 mo (n = 2292)	
Background characteristic	no. (%)	No. (%)	*P* value	No. (%)	*P* value	No. (%)	*P* value	No. (%)	*P* value
Sex of child			**<.001**		**.02**		.46		.23
Boy	1646 (52)	758 (39)		1190 (61)		1265 (65)		1102 (64)	
Girl	1496 (48)	580 (33)		1009 (58)		1120 (64)		1190 (62)	
No. of siblings			**<.001**		**<.001**		**<.001**		**<.001**
None	1417 (45)	635 (39)		1038 (65)		1163 (72)		1020 (63)	
1	987 (31)	427 (37)		679 (59)		767 (66)		745 (65)	
2	421 (13)	159 (32)		264 (54)		280 (57)		299 (62)	
≥3	258 (8)	81 (23)		160 (46)		119 (35)		179 (53)	
Missing information	59 (2)								
Parental asthma			.31		.37		.14		**.04**
No	2577 (82)	863 (34)		1463 (58)		1653 (65)		1588 (63)	
Yes	497 (16)	178 (36)		292 (60)		301 (62)		282 (58)	
Missing information	68 (2)								
Parental allergic rhinitis			.99		.77		.30		.11
No	1022 (33)	353 (35)		590 (59)		662 (66)		641 (64)	
Yes	1956 (62)	677 (35)		1117 (58)		1228 (64)		1169 (61)	
Missing information	164 (5)								
Place of birth			**<.001**		**<.001**		.12		.07
Region of Tampere	1887 (60)	602 (31)		1076 (55)		1277 (66)		1181 (61)	
Region of Oulu	1255 (40)	736 (42)		1123 (64)		1108 (63)		1111 (64)	
Maternal smoking during pregnancy			**<.001**		**<.001**		**<.001**		**.002**
No	2811 (89)	1106 (34)		1878 (57)		2084 (64)		2010 (62)	
Yes	229 (8)	182 (60)		245 (82)		229 (77)		207 (71)	
Missing information	102 (3)								
Season of birth			.09		.32		.44		.64
Spring (April-May)	551 (18)	221 (34)		384 (59)		412 (63)		411 (64)	
Summer (June-August)	822 (26)	371 (38)		565 (59)		617 (64)		595 (62)	
Autumn (September-November)	732 (23)	332 (38)		544 (62)		584 (66)		530 (61)	
Winter (December-March)	1037 (33)	414 (34)		706 (59)		772 (64)		756 (63)	
Duration of gestation (wk)			.97		.12		.50		**<.001**
First quarter: <39	700 (22)	296 (36)		507 (62)		524 (64)		467 (57)	
Second quarter: 39	804 (26)	345 (36)		549 (57)		615 (64)		589 (62)	
Third quarter: 40-40.9	780 (25)	330 (36)		532 (58)		590 (65)		583 (64)	
Fourth quarter: >40.9	827 (6)	353 (37)		585 (61)		637 (67)		630 (66)	
Missing information	31 (1)								
Maternal age (y)			**<.001**		**<.001**		**<.001**		**<.001**
<25	466 (15)	277 (47)		405 (70)		409 (71)		402 (70)	
25-29	1099 (35)	483 (38)		785 (62)		857 (67)		815 (64)	
30-34	972 (31)	359 (32)		645 (57)		705 (63)		686 (61)	
>35	605 (19)	219 (30)		364 (51)		414 (58)		389 (55)	
Maternal basic education			**<.001**		**<.001**		.16		.11
Less than high school	1264 (40)	673 (44)		1012 (67)		999 (66)		963 (64)	
High school	1795 (57)	617 (30)		1114 (54)		1307 (64)		1260 (62)	
Missing information	83 (3)								
Pets at home during first year of life			**<.001**		**.01**		**<.001**		**<.001**
No	2099 (67)	675 (33)		1163 (57)		1285 (63)		1128 (60)	
Yes	953 (30)	369 (39)		577 (62)		658 (70)		634 (68)	
Missing information	90 (3)								
Family farming or child visited stable during first year of life			.06		.13		.54		.47
No	2437 (78)	812 (34)		1373 (57)		1560 (65)		1478 (62)	
Yes	603 (19)	225 (38)		360 (61)		378 (64)		375 (64)	
Missing information	102 (3)								
Mode of delivery			.27		**.004**		.25		.20
Normal	2700 (86)	1127 (36)		1844 (59)		2028 (64)		1970 (63)	
Cesarean section	420 (13)	199 (38)		335 (65)		344 (67)		306 (60)	
Missing information	22 (1)								

(Continued)

TABLE II. *(Continued)*

Background characteristic	Frequency (n = 3142), no. (%)	Food diversity at 3, 4, 6, and 12 mo: ≥2 food items at 3 mo (n = 1338)		≥4 food items at 4 mo (n = 2199)		≥8 food items at 6 mo (n = 2385)		≥11 food items at 12 mo (n = 2292)	
		No. (%)	*P* value	No. (%)	*P* value	No. (%)	*P* value	No. (%)	*P* value
Birth weight			.68		.35		.43		.82
First quarter	763 (24)	319 (35)		550 (61)		600 (67)		565 (63)	
Second quarter	781 (25)	322 (35)		536 (58)		579 (63)		577 (63)	
Third quarter	780 (25)	336 (36)		532 (58)		598 (65)		564 (61)	
Fourth quarter	796 (25)	349 (37)		561 (61)		595 (64)		570 (62)	
Missing information	22 (1)								

P values in boldface indicate statistical significance.

TABLE III. Associations between food diversity at 3, 4, 6, and 12 months and the incidence of asthma by 5 years of age

Diversity of single food items at 3, 4, 6, and 12 mo	Frequency (n = 3142), no. (%)*	Any asthma (n = 194), HR (95% CI)		Atopic asthma (n = 107), HR (95% CI)		Nonatopic asthma (n = 79), HR (95% CI)	
		Unadjusted	Adjusted†	Unadjusted	Adjusted†	Unadjusted	Adjusted†
At 3 mo							
No food	944 (30)	0.80 (0.55-1.18)	0.83 (0.53-1.28)	1.01 (0.60-1.70)	1.21 (0.65-2.26)	0.66 (0.37-1.19)	0.60 (0.32-1.13)
1-2 food items	1410 (45)	0.84 (0.59-1.19)	0.82 (0.56-1.21)	0.98 (0.60-1.59)	1.13 (0.65-1.97)	0.64 (0.37-1.08)	0.55 (0.31-0.97)
>2 food items	751 (24)	1	1	1	1	1	1
P value		.48	.57	.99	.83	.21	.10
At 4 mo							
No food	357 (11)	1.04 (0.66-1.66)	1.07 (0.63-1.82)	1.13 (0.58-2.23)	1.26 (0.56-2.83)	1.04 (0.55-2.00)	1.02 (0.50-2.07)
1-2 food items	543 (17)	0.77 (0.49-1.20)	0.83 (0.51-1.35)	1.21 (0.68-2.14)	1.55 (0.83-2.91)	0.28 (0.11-0.72)	**0.26 (0.09-0.75)**
3-4 food items	1016 (32)	0.97 (0.69-1.35)	0.99 (0.68-1.43)	1.45 (0.92-2.29)	1.62 (0.98-2.70)	0.60 (0.35-1.02)	0.57 (0.32-1.02)
>4 food items	1189 (38)	1	1	1	1	1	1
P value		.66	.85	.46	.27	.02	**.03**
At 6 mo							
0-4 food items	183 (6)	1.92 (1.08-3.40)	1.75 (0.88-3.45)	2.40 (1.12-5.13)	**2.52 (1.01-6.29)**	1.33 (0.50-3.50)	0.90 (0.28-2.92)
5-6 food items	405 (13)	1.28 (0.80-2.06)	1.51 (0.90-2.51)	1.85 (1.01-3.40)	**2.43 (1.23-4.82)**	0.72 (0.31-1.67)	0.70 (0.29-1.69)
7-8 food items	1527 (49)	1.24 (0.88-1.76)	1.27 (0.86-1.87)	1.42 (0.87-2.30)	1.45 (0.83-2.55)	1.09 (0.65-1.83)	1.08 (0.61-1.91)
>8 food items	990 (32)	1	1	1	1	1	1
P value		.16	.27	.08	**.04**	.71	.80
At 12 mo							
0-7 food items	133 (4)	**2.84 (2.26-6.52)**	**4.19 (2.31-7.58)**	**4.45 (2.19-9.05)**	**5.17 (2.34-11.42)**	**2.84 (1.18-6.84)**	2.94 (1.11-7.84)
8-9 food items	429 (14)	**1.66 (1.09-2.52)**	**1.87 (1.17-2.98)**	**2.34 (1.37-3.98)**	**2.93 (1.60-5.37)**	0.80 (0.36-1.77)	0.76 (0.32-1.78)
10-11 food items	1398 (44)	0.96 (0.68-1.37)	1.03 (0.69-1.54)	1.04 (0.64-1.69)	1.21 (0.69-2.12)	0.85 (0.50-1.45)	0.85 (0.47-1.55)
>11 food items	1145 (36)	1	1	1	1	1	1
P value		**<.001**	**<.001**	**<.001**	**<.001**	**.05**	.07

Values in boldface indicate statistical significance.

HR, Hazard ratio.

*Missing was 37 (1%) for the food items at each month.

†Adjusted for sex of child, number of siblings, parental asthma, parental rhinitis, place of birth, maternal smoking during pregnancy, season of birth, duration of gestation, maternal age, maternal basic education, pets at home by 1 year, family farming or child's visit to a stable during the first year of life, mode of delivery, and birth weight.

that less food diversity at 12 months of age was associated with an increased risk of any asthma, atopic asthma, wheeze, and allergic rhinitis among children with a parental history of allergy. Less food diversity at 6 months of age was additionally associated with an increased risk of allergic rhinitis among children with a parental history of allergy.

DISCUSSION

By 3 and 4 months of age, the diversity of foods was not associated with the risk of asthma and allergies in childhood. By 6 months of age, less diversity of foods was associated with increased risk of allergic rhinitis but not with other end points. By 12 months of age, less diversity of foods was associated with increased risk of any asthma, atopic asthma, wheeze, and allergic rhinitis. In stratified analyses the associations between food diversity and the end points tended to be different in some cases between children with and without early manifestation of atopic eczema on the one hand and between children with and without a parental history of allergy on the other, indicating a potential for reverse causality in our study.

In line with recent suggestions that early complementary feeding might protect against the risk of atopic diseases,[21-34] our current findings complement this evidence base by showing that the diversity of foods during infancy plays a role in the development of allergies. Although we did not observe any association with food diversity at 3 and 4 months of age, some effects were seen starting from 6 months of age and became more apparent by 12 months of age. On the basis of our previous findings[31-34] and other studies on the timing of infant feeding,[21-30] it seems likely that although the systematic introduction of single complementary foods one at a time seems more important before

TABLE IV. Associations between food diversity at 3, 4, 6, and 12 months and the risk of wheeze, atopic eczema, and allergic rhinitis by 5 years of age

Diversity of single food items at 3, 4, 6, and 12 mo	Frequency (n = 3142, no. (%)*)	Wheeze (n = 847), OR (95% CI)		Atopic eczema (n = 785), OR (95% CI)		Allergic rhinitis (n = 442), OR (95% CI)	
		Unadjusted	Adjusted†	Unadjusted	Adjusted†	Unadjusted	Adjusted†
At 3 mo							
No food	944 (30)	0.90 (0.69-1.18)	0.85 (0.63-1.16)	0.90 (0.71-1.15)	0.93 (0.71-1.22)	0.92 (0.67-1.26)	1.00 (0.69-1.46)
1-2 food items	1410 (45)	0.96 (0.75-1.22)	0.92 (0.70-1.21)	0.77 (0.62-0.96)	0.79 (0.62-1.01)	0.77 (0.57-1.04)	0.87 (0.62-1.23)
>2 food items	751 (24)	1	1	1	1	1	1
P value		.73	.59	.06	.14	.21	.60
At 4 mo							
No food	357 (11)	1.00 (0.71-1.40)	1.04 (0.71-1.53)	0.97 (0.71-1.33)	0.95 (0.66-1.36)	1.02 (0.68-1.53)	1.08 (0.68-1.71)
1-2 food items	543 (17)	1.08 (0.81-1.43)	1.01 (0.74-1.39)	0.80 (0.61-1.06)	0.89 (0.66-1.21)	1.12 (0.80-1.58)	1.31 (0.89-1.93)
3-4 food items	1016 (32)	1.08 (0.86-1.37)	1.11 (0.85-1.44)	0.90 (0.72-1.12)	0.96 (0.75-1.23)	0.86 (0.64-1.17)	1.00 (0.72-1.39)
>4 food items	1189 (38)	1	1	1	1	1	1
P value		.90	.89	.42	.90	.53	.55
At 6 mo							
0-4 food items	183 (6)	1.56 (1.00-2.43)	1.59 (0.95-2.67)	1.39 (0.88-2.19)	1.36 (0.78-2.36)	**1.97 (1.18-3.29)**	**2.16 (1.20-3.89)**
5-6 food items	405 (13)	1.34 (0.97-1.84)	1.46 (1.01-2.09)	**1.32 (0.96-1.81)**	1.48 (1.04-2.12)	**1.73 (1.17-2.56)**	**1.91 (1.24-2.95)**
7-8 food items	1527 (49)	1.24 (0.99-1.57)	1.25 (0.96-1.61)	**1.38 (1.11-1.71)**	1.36 (1.06-1.72)	**1.42 (1.05-1.92)**	1.34 (0.97-1.86)
>8 food items	990 (32)	1	1	1	1	1	1
P value		.10	.11	**.03**	.05	**.01**	**.02**
At 12 mo							
0-7 food items	133 (4)	**2.76 (1.68-4.55)**	**2.49 (1.47-4.24)**	1.05 (0.47-2.34)	0.99 (0.42-2.33)	**3.52 (2.03-6.11)**	**3.10 (1.66-5.78)**
8-9 food items	429 (14)	**1.39 (1.03-1.89)**	1.38 (0.99-1.92)	1.35 (0.94-1.93)	1.35 (0.91-2.01)	**2.40 (1.68-3.42)**	**2.43 (1.63-3.63)**
10-11 food items	1398 (44)	1.01 (0.80-1.27)	0.96 (0.74-1.25)	1.18 (0.93-1.51)	1.20 (0.92-1.56)	1.28 (0.95-1.72)	1.34 (0.96-1.86)
>11 food items	1145 (36)	1	1	1	1	1	1
P value		**.004**	**.008**	.34	.41	**<.001**	**<.001**

Values in boldface indicate statistical significance.
OR, Odds ratio.
*Missing was 37 (1%) for the food items at each month.
†Adjusted for sex of child, number of siblings, parental asthma, parental rhinitis, place of birth, maternal smoking during pregnancy, season of birth, duration of gestation, maternal age, maternal basic education, pets at home by 1 year, family farming or child's visit to a stable during the first year of life, mode of delivery, and birth weight.

6 months of age, more diverse foods might be important beyond 6 months of age.

Of the 2 previous studies that have examined the role of food diversity during infancy in the development of atopic diseases, less food diversity at 6 months of age was associated with a decreased risk of atopic dermatitis at age 2 years but not with asthma, allergic rhinitis, atopic dermatitis, and atopy at 6 years of age in one study.[22,23] However, less food diversity at 6 and 12 months of age was associated with an increased risk of atopic dermatitis in 4-year-old children in the more recent study.[35] In the first study from Germany,[22] evidence contrary to our study was observed for food diversity when the children were 2 years old, and this discrepancy might be due to the age difference between our cohort and the cohort in that study. In addition, food diversity was assessed only up to the age of 6 months but not after in that study, which might explain the reason for the null associations with the end points when the children were 6 years old.[23] In our study the effect of food diversity was most obvious at 12 months but less so before that age. The results of the second study[35] are in agreement with our findings, although only atopic dermatitis was examined in that study. In our recent report based on the same children of the current study population, less food diversity as early as 3 months of age was associated with increased risk of sensitization to specific food and inhalant allergens at the age of 5 years.[34]

The emerging evidence challenges the long-held thinking that the gut mucosa of the infant is immature during infancy and on exposure to certain environmental antigens, with diet being a key factor, might increase the likelihood of sensitization and subsequent development of allergy.[43,44] However, the putative effect of the food antigens in the maturation processes of the gut microbiota is unclear.[43] Further immunologic studies might provide clearer insights into the maturation processes of the gut immune system during infancy and its interaction with environmental factors, such as early-life food antigens, in promoting or protecting against the risk of allergies. According to the hygiene hypothesis, reduced microbial antigen exposure, possibly in interaction with environmental antigens during infancy, might affect the maturation of the immune system in such a way that the subsequent development of immune-mediate ailments during childhood is favored.[44,45]

In a recent study it was shown that breast-feeding modified the diversity of the intestinal microbiota in Canadian infants.[12] Although the duration of breast-feeding did not modify the associations between food diversity and the allergic end points in our study, it would be informative to ascertain whether the role of food diversity in promoting or protecting against the risk of asthma and allergies in childhood is also modified by the microbial composition of the gut microbiota. We did not have any measure of the microbial composition of the gut microbiota in these children; hence we were unable to assess the potential modification of the effects of food diversity on the risk of asthma and allergies by microbial factors.

The asthma and allergic end points in our study were assessed by using the standardized ISAAC questionnaire, which has been validated for the asthma component.[40] The study had a

prospective design, hence being appropriate for studying the temporal associations between food diversity and the end points. The subjects were recruited among children carrying genetic risk (HLA-conferred susceptibility) for type 1 diabetes. This could limit the generalizability of our findings to the general population. Although some HLA genes have been associated with the risk of allergies,[46,47] other studies have found no association.[48,49] The absolute risk of type 1 diabetes in the DIPP cohort is in the range of 3% to 4% by the age of 15 years, whereas it is about 0.7% in the general Finnish population.[36] However, our study population was not selected on the basis of family history of allergies. The cumulative incidence of allergic rhinitis (14%) and asthma (6%) in our study population is similar to that seen in earlier studies in the Finnish population of similar age, reporting a frequency of 15% to 16% for allergic rhinitis[39] and 5% for asthma.[50]

The number of statistical tests performed could mean that our type 1 error rate might not be at the 0.05 level. Nevertheless, we have taken multiplicity issues into account in cautious interpretation of the results, emphasizing the findings with *P* values substantially smaller than .05 as meaningful. The ascertainment of food diversity in our study was based on the number of complementary foods the child had received at defined time points in parallel to the approach in previous surveys. We think that the definition of food diversity might be enhanced by incorporating a wider spectrum of the infant's diet, including use of supplements and other micronutrients (both intake and serum levels).

In conclusion, less diversity of foods by 6 and 12 months of age was associated with an increased risk of asthma and allergic diseases in childhood. The mechanisms for this association are unclear, but potential links include higher diversity of the gut microbiome or the food antigen exposure. The results also highlight that in addition to the benefits conferred by early exposure to complementary foods for the development of allergies, higher diversity of foods during infancy is advantageous as well.

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Key messages

- **Less food diversity during the first year of life appears to increase the risk of asthma and allergies in childhood.**
- **The current results seem to highlight that exposure to diverse food antigens during early life might enhance the development of immune tolerance.**
- **In addition to the benefits of early introduction of complementary foods for the development of allergies, high food diversity during infancy might be equally advantageous.**

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