Original Article

Different Measures of Diet Diversity During Infancy and the Association with Childhood Food Allergy in a UK Birth Cohort Study

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What is already known about this topic? Diet diversity (DD) during infancy may be beneficial for future health.

What does this article add to our knowledge? Increased DD measured using 4 different methods from 6 months onward, in the first year of life, may decrease the likelihood of food allergies over the first decade. However, DD at 3 months showed no significant effect on food allergy outcomes.

How does this study impact current management guidelines? These findings support the recommendation that early oral intake of a variety of foods and food allergens, once the infant is developmentally ready, will reduce incidence of food allergy in the first 10 years of life.

BACKGROUND: Diet diversity (DD) during infancy may prevent food allergies (FA), possibly by exposing the gastrointestinal microbiota to diverse foods and nutrients.
OBJECTIVE: To investigate the association between 4 different measures of DD during infancy and development of FA over the first decade of life.
METHODS: A birth cohort born between 2001 and 2002 were followed prospectively, providing information on sociodemographic, environmental, and dietary exposures. Information on age of introduction of a range of foods and food allergens was collected during infancy. Children were assessed for FA at 1, 2, 3, and 10 years. DD was defined using 4 measures in the first year of life: the World Health Organization definition of minimum DD at 6 months, as food diversity (FD) and fruit and vegetable diversity (FVD) at 3, 6, and 9 months, and as food allergen diversity (FAD) at 3, 6, 9, and 12 months.
RESULTS: A total of 969 pregnant women were recruited at 12-week gestation. A total of 900, 858, 891, and 827 offspring were assessed at 1, 2, 3, and 10 years. Univariate analysis showed that World Health Organization DD ($P = .0047$), FD ($P = .0009$), FAD ($P = .0048$), and FVD ($P = .0174$) at 6 months and FD ($P = .0392$), FAD ($P = .0233$), and FVD (.0163) at 9 months significantly reduced the odds of FA over the first decade of life. DD measures at 3 months were not associated with FA, but only 33% of the cohort had solid foods introduced by this age.
CONCLUSION: Increased infant DD, as measured by 4 different methods, decreased the likelihood of developing FA. © 2020 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2020;8:2017-26)

Key words: *Dietary variety; Diet diversity; Eczema; Infant feeding; Food allergy prevention*

"Diet diversity" (DD) is defined as the number of different foods or food groups consumed over a given reference period.[1] DD can also be defined in terms of diversity of foods eaten (FD), number of foods within a food group consumed, for

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Abbreviations used
CI- Confidence interval
DD- Diet diversity
FA- Food allergy
FAD- Food allergen diversity
FD- Food diversity
FLG-LOF- Filaggrin loss-of-function
FVD- Fruit and vegetable diversity
ISAAC- International Study of Allergy and Asthma in Childhood
OFC- Oral food challenge
OR- Odds ratio
SPT- Skin prick test
WHO- World Health Organization

example, fruit and vegetable diversity (FVD), using the World Health Organization (WHO) definition of minimum DD, or the number of allergens being consumed, referred to as food allergen diversity (FAD).

Recently there has been considerable interest in the effect of infant DD in the prevention of allergic disease. A task force report from the European Academy of Asthma, Allergy, and Immunology suggested that increased DD may reduce the risk for allergy development via its effect on the microbiome, increased intake of nutrients related to allergy prevention, and increased exposure to allergens.[2] The report summarized 14 papers reporting the role of DD on allergy outcomes. However, only 1 study reported on the association between DD and food allergy (FA) outcomes, suggesting that increased DD in infancy may reduce the risk of FA.[3]

The aim of this study is to assess the effect of infant DD in the first year of life on FA outcomes over the first 10 years of life in a population birth cohort.

MATERIALS AND METHODS

The Food Allergy and Intolerance Research birth cohort included children born in the Isle of Wight (UK) (n = 969) between 2001 and 2002 who were followed up prospectively.[4,5] Demographic and reported allergy data were collected at 12-week gestation, at birth, and during subsequent follow-up studies at set time periods.

Dietary data

Infant feeding data were collected via a standardized questionnaire at ages 3, 6, 9, and 12 months.[6] Specific information was collected regarding breastfeeding duration, introduction of bottle feeding, and age of introduction of 21 different foods, categorized into time periods of <3 months (by 3 months), 3 to 6 months (by 6 months), and 6 to 9 months (by 9 months). At the 12-month visit, parents were asked questions regarding introduction of 8 allergenic foods (dairy, whole egg, wheat, soya, peanut, tree nuts, fish, and sesame) during the first year of life.[7]

Diet diversity

DD was calculated according to the available information at the different time points and was defined as follows:

(1) Calculating minimum DD according to the WHO classification. This is a population-level indicator designed by the WHO to assess DD as part of infant and young child feeding practices among children aged 6 to 23 months. It is calculated by summing the number of food groups included in the child's diet at 6 months (*maximum count of 7*). The 7 food groups included are grains/roots/tubers, legumes/nuts, dairy, flesh foods, eggs, vitamin A−rich fruit and vegetables, other fruit and vegetables.[8]
(2) Summing the number of foods introduced at each time point;[3,9] therefore, the *maximum score was 21* at 3, 6, and 9 months, referred to as FD.
(3) Summing the number of fruits and vegetables introduced at each time point (non-citrus fruits, citrus fruits, strawberry, vegetables not including potato and tomato) was used to compute a FVD score at 3, 6, and 9 months.[4]
(4) Summing the number of main food allergens introduced at 3, 6, 9, and 12 months out of a total score of 8 (milk, egg, wheat, fish, soy, peanut, tree nuts, and sesame), referred to a FAD.[2,10]

DD scores did not take into account frequency of intake or portion size consumed.

Food allergy diagnosis

Children were clinically examined and skin prick tests (SPTs) were performed to milk, wheat, egg, cod, peanut, and sesame at 1, 2, 3, and 10 years, as previously described.[4,5]

FA was defined as a positive food challenge or a positive SPT and a convincing clinical history, as previously reported. Children were invited for oral food challenges (OFCs) according to predefined criteria. Children were invited for a food challenge if they were sensitized to a food that they have never knowingly consumed or a reported adverse reaction to a food irrespective of their sensitization status. OFCs at 1, 2, and 3 years were performed following a previously published algorithm.[4,5,7] All eligible children underwent open OFCs. Those with a history of immediate symptoms from prior ingestion of the food underwent a hospital challenge. For safety reasons, in some instances, challenges were not conducted (eg, if there was a clear history of a systemic reaction in addition to sensitization). Challenges were performed at home for participants with a negative SPT and delayed symptoms. Only those with a positive reaction were invited to participate in a double-blind, placebo-controlled, food challenge. At 10 years of age, the PRACTALL recommendations for food challenge doses were followed.[11] FA outcomes are described at ages 1, 2, 3, and 10 years. A new variable was calculated for children diagnosed with any FA in the first 10 years of life, referred to as "over the first 10 years."

Diagnosis of eczema

The presence of eczema was recorded via parental report using questions from the International Study of Asthma and Allergy in Children (ISAAC study)[12] at ages 3, 6, 9, and 12 months, and 2, 3, and 10 years.[4,5,7] We used the question: Has your child been diagnosed with eczema?

Filaggrin loss-of-function

DNA was extracted from umbilical cord blood and was genotyped for 4 FLG null variants common among Europeans: R501X, S3247X, R2247X, and 2282del4. Genotyping was performed using TaqMan allelic discrimination assays, as previously described,[13] with PerfeCTa mastermix (VWR International, Radnor, Pa) and 5 ng DNA per sample. Control samples of known genotype were included to allow end-point genotype determination. Individuals carrying the minor allele for at least one of the FLG variants were classified as filaggrin haploinsufficient.

Demographic information

Data regarding race/ethnicity, parity, maternal education, and socioeconomic status were collected by questionnaire. Self-reported

TABLE I. Participant demographic characteristics

Characteristic	n (%)
Male (n = 969)	492 (50.8)
Number of participants first born in family (n = 969)	401 (41.2)
Type of delivery (n = 969)	755 (77.9) normal 211 (21.8) cesarean 3 (0.3) (missing)
Family history of allergy at recruitment; asthma, eczema, rhinitis, food allergy (n = 969)	788 (81.3)
Maternal history of allergy at recruitment; asthma, eczema, rhinitis, food allergy (n = 969)	558 (57.6)
Maternal FA at recruitment (n = 969)	189 (19.5)
Maternal education at recruitment (n = 969)	
No education	12 (1.2)
Secondary school education (up to 16 y of age)	363 (37.5)
Postsecondary school education (between 16 and 18 y of age)	437 (45.1)
Third-level education (18 y of age)	152 (15.7)
Median breastfeeding duration in days (IQR)	35 (1, 154)
Any breastfeeding; even just 1 feed (n = 969)	743 (76.7)
Median age of introduction of solid foods in weeks (IQR)	16 (13, 16)
Number of infants introducing solids by 3 m (n = 925)	207 (22.4)
Median age of introduction of infant formula in days (IQR)	14 (0, 56)
Eczema at 3 mo (n = 927)	200 (21.6)
Eczema at 6 mo (n = 918)	424 (42.8)
Eczema at 12 mo (n = 932)	535 (57.4)
Diagnosed FA at 1 y* (n = 969)	39 (4.0)
Any reported allergy at 1 y (asthma, eczema, rhinitis, food allergy)	496 (51.2)
Diagnosed FA at 2 y* (n = 858)	21 (2.5)
Any reported allergy at 2 y (asthma, eczema, rhinitis, food allergy) (n = 858)	498 (55.9)
Diagnosed FA at 3 y (n = 891)	27 (3.0)
Any reported allergy at 3 y (asthma, eczema, rhinitis, food allergy) (n = 891)	409 (45.9)
Diagnosed FA at 10 y* (n = 827)	30 (3.6)
Any reported allergy at 10 y (asthma, eczema, rhinitis, food allergy) (n = 827)	434 (52.5)
Any food allergy over the first 10 y of life (n = 947)	64 (6.8)
Any reported allergy over the first 10 y of life (n = 947)	809 (86.4)
Any filaggrin mutation (n = 296)	35 (11.8)

FA, Food allergy; *IQR*, interquartile range.
*Includes both IgE and non-IgE FA.

history of maternal and family allergies, such as asthma, eczema, rhinitis, or food allergy, was collected at recruitment using the ISAAC questions.[12]

Statistical methods

Data were double entered by different operators on SPSS versions 20 and 21 (SPSS Inc., Chicago, Ill). Descriptive statistics with means (standard deviations) or counts (frequencies) were calculated. Univariate analysis was carried out to assess the association of each DD measure and FA outcome.

Logistic regression models were fitted to describe the relationship between the binary FA variables, FD measures, and other related covariates. If independent variables were found to be statistically significant at the $P = .05$ level in the univariate analysis, the variables were entered into a multivariate model to understand the variables at each time point that are independently associated with FA in the first 10 years of life. Spearman correlations were performed to examine relationships between count data. We therefore only performed multivariate analyses if the food count variable was significantly associated with the outcome variable at the $P = .05$ level in the univariate analysis, because we were more interested in the FD values than other independent variables. All significance tests were 2 sided and analyses were performed with SAS version 9.4 (SAS Institute Inc., Cary, NC). We made no adjustments for multiple comparisons in this study because the hypotheses were made *a priori*, and the hypotheses ask the same core question in different ways.

To test whether eczema was a confounder in the relationship between DD and FA at the time points we were investigating, we examined whether FA were associated with eczema and whether DD was associated with eczema. If these associations were significant at the $P < .05$ level and the estimate for the relationship between DD and FA at each time point changed by more than 10% with eczema included and excluded from the model, eczema was acknowledged as a confounder. We also tested for other possible confounders such as age of introduction of solid foods and DD and eczema. To understand the role of filaggrin loss-of-function (FLG-LOF) in any of the associations seen, we also tested for FLG-LOF outcomes and FA and association between FLG-LOF outcomes and eczema. Finally, we tested for an interaction between FD, FLG-LOF, and eczema in the logistic regression modeling with FA outcomes.

Ethical approval was obtained from the NRES South Central—Southampton B Research Ethics Committee (REF 10/H0504/11). All parents consented and children provided assent.

RESULTS

Study sample

For the primary analysis, we included N = 969 mother-infant dyads with information on diet, eczema, and FA outcomes. For the secondary analysis, we included N = 296 children with available DNA and information on 4 filaggrin LOF variants (2282del4, R501X, S3247X, and R2247X). The study population consisted of 969 children. Nine hundred (92.9%) children were seen at 1 year, 858 (88.5%) at 2 years, 891 (91.9%) at 3 years, and 827 of 969 (85%) children were seen at 10 years. Over the course of the 10 years, 947 of 969 (97.7%) children were seen at any time point.[4-7] Demographic, environmental, and allergic characteristics of participants are shown in Table I.

Association of background characteristics with food allergy

Family history or maternal history of allergy was not associated with FA outcomes in the child at any time point (Table II). Maternal history of FA increased the odds of having an FA at 2 years (odds ratio [OR]: 2.588, 95% confidence interval [CI]: 1.055-6.348, $P = .038$) and 10 years (OR: 3.061, 95% CI: 1.442-6.497, $P = .0036$), but not at 1, 3, and over the first 10 years of life. Parity did not show an association with FA outcomes at any time point other than at 10 years, with an increased number of older siblings reducing the odds of developing an FA (OR: 0.499, 95% CI: 0.295-0.845, $P = .0096$). Breastfeeding duration did not affect FA outcomes at any time point, but later

TABLE II. Association between food allergy outcomes, family history of allergic disease, maternal history of allergic disease, maternal history of food allergy, parity, and eczema in the first year of life

	Food allergy	OR (95% CI)	*P* value
Family history of allergic disease	1 y	1.58 (0.6-4.1)	.35
	2 y	4.54 (0.6-34.1)	.14
	3 y	1.85 (0.5-6.2)	.32
	10 y	1.57 (0.5-4.5)	.41
	Over first 10 y	1.93 (0.9-4.3)	.11
Maternal history of allergic disease	1 y	1.33 (0.7-2.6)	.40
	2 y	2.37 (0.9-6.5)	.10
	3 y	1.24 (0.6-2.7)	.60
	10 y	1.80 (0.8-4.0)	.14
	Over first 10 y	1.42 (0.8-2.4)	.20
Maternal history of FA	1 y	1.88 (0.9-3.8)	.08
	2 y	2.59 (1.1-6.3)	*.04*
	3 y	1.40 (0.6-3.4)	.45
	10 y	3.06 (1.4-6.5)	*.004*
	Over first 10 y	1.69 (1.0-3.0)	.07
Parity	1 y	0.76 (0.5-1.1)	.13
	2 y	0.77 (0.5-1.2)	.28
	3 y	0.84 (0.6-1.2)	.38
	10 y	0.50 (0.3-0.8)	*.01*
	Over first 10 y	0.77 (0.6-1.0)	.06
Breastfeeding duration (d)	FA year 1	1.00 (1.0-1.0)	.16
	FA year 2	1.00 (1.0-1.0)	.17
	FA year 3	1.00 (1.0-1.0)	.45
	FA year 10	1.00 (1.0-1.0)	.11
	FA over 10	1.00 (1.0-1.0)	.08
Age of introduction of solid foods (wk)	FA year 1	1.22 (1.1-1.4)	*.001*
	FA year 2	1.15 (0.9-1.3)	.07
	FA year 3	1.08 (0.9-1.2)	.28
	FA year 10	1.09 (0.9-1.2)	.21
	FA over 10	1.16 (1.1-1.3)	*.002*
Any eczema in first year of life	1 y	2.73 (1.2-6.3)	*.02*
	2 y	12.01 (1.6-89.9)	*.02*
	3 y	3.23 (1.1-9.4)	*.03*
	10 y	2.78 (1.1-7.3)	*.03*
	Over first 10 y	2.82 (1.5-5.5)	*.002*

CI, Confidence interval; *FA*, food allergy; *OR*, odds ratio.
Italicized text indicates statistical significance ($P < .05$).

introduction of solids (continuous variable measured in weeks; Table II) increased the odds of having an FA at 1 year (OR: 1.215, 95% CI: 1.087-1.359, $P = .0006$) and an FA over the first 10 years of life (OR: 1.157, 95% CI: 1.056-1.269, $P = .0019$). Any eczema in the first year of life (3, 6, 9, or 12 months) was significantly associated with FA outcomes at 1 year (OR: 2.731, 95% CI: 1.192-6.257, $P = .018$), 2 years (OR: 12.015, 95% CI: 1.605-89.959, $P = .015$), 3 years (OR: 3.23, 95% CI: 1.106-9.426, $P = .032$), 10 years (OR: 3.230, 95% CI: 1.107-9.426, $P = .0319$), and over the first 10 years of life (OR: 2.823, 95% CI: 1.453-5.483, $P = .0022$).

There was also no association between parity and FD at 6 months (Spearman's correlation $P = .25$).

Association between diet diversity score and FA outcomes

The median number of foods introduced by certain age categories according to the 4 measures of DD (minimum diversity according to the WHO, FD, FAD, and FVD) is shown in Table III. Table IV shows the univariate results for the associations between DD and FA at years 1, 2, 3, 10, and over 10 years of age.

DD according to the WHO Minimum Diet Diversity score

DD by 6 months, when classified according the WHO definition, reduced the odds of having an FA significantly at all time points other than 2 years.

Classifying DD according to number of foods introduced

By 3 months, DD did not show an association with FA at any of the time points studied, though 33% of infants had been introduced to solids by 12 weeks (Table I). By 6 months, increased DD showed a reduced odds of developing FA at 1, 3, 10, and over the first 10 years of life but not at 2 years (Figure 1). By 9 months, the number of foods introduced showed a reduced odds for the development of FA at 2, 3, and 10 years of age and over the first 10 years of life but not at 1 year of age.

Classifying DD according to number of allergenic foods introduced

As with FD at 3 months, FAD at 3 months did not show any association with FA outcomes at any time point studied. FAD at 6 months showed a reduced odds of developing FA at 1 year and over the first 10 years of life but not at 2, 3, and 10 years (Figure 2). Similarly, FAD at 9 months showed a reduced odds of developing FA by 1, 3, and over the first 10 years of life but not at 2 and 10 years. Atopic dermatitis at 6 and 9 months was

TABLE III. Diet diversity score at each time point

Age range	Median WHO DD score (IQR, minimum-maximum)	Median food DD score (IQR, minimum-maximum)	Median FAD score (IQR, minimum-maximum)	Median FVD score (IQR, minimum-maximum)
By 3 mo*	NA	0 (0, 0-15)	0 (0, 0-3)	0 (0, 0-4)
By 6 mo*	5 (3-4, 0-5)	11 (9-13, 0-21)	2 (2-3, 0-6)	3 (3-4, 0-5)
By 9 mo*	NA	16 (14-17, 5-21)	4 (1-8, 3-4)	5 (4-5, 1-5)
By 12 mo†	NA	NA	5 (4-6, 0-8)	NA

DD, Diet diversity; *FAD*, food allergen diversity; *FVD*, fruit and vegetable diversity; *IQR*, interquartile range; *N/A*, not applicable (not calculated at 3 and 9 months); *WHO*, World Health Organization.
*21 foods included in questionnaire at 3, 6, and 9 months.
†Only allergen intake reported.

TABLE IV. Measures of diet diversity vs food allergy outcomes over the first 10 years of life using univariate analysis

	OR (95% CI)	*P* value
WHO DD at 6 mo		
1 y	0.77 (0.6-0.9)	*.004*
2 y	0.78 (0.61-1.0)	.05
3 y	0.71 (0.6-0.9)	*.001*
10 y	0.75 (0.6-0.9)	*.01*
Over first 10 y	0.80 (0.7-0.9)	*.005*
Number of foods at 3 mo		
1 y	0.73 (0.4-1.3)	.25
2 y	0.80 (0.4-1.5)	.50
3 y	1.05 (0.8-1.4)	.76
10 y	0.98 (0.7-1.4)	.90
Over first 10 y	0.84 (0.6-1.2)	.30
Number of foods by 6 mo		
1 y	0.83 (0.8-0.9)	*.0004*
2 y	0.88 (0.8-1.01)	.07
3 y	0.85 (0.7-0.9)	*.007*
10 y	0.88 (0.8-0.9)	*.03*
Over first 10 y	0.87 (0.8-0.9)	*.001*
Number of foods by 9 mo		
1 y	0.89 (0.8-1.0)	.13
2 y	0.81 (0.7-0.9)	*.02*
3 y	0.8 (0.7-0.9)	*.007*
10 y	0.81 (0.7-0.9)	*.007*
Over first 10 y	0.9 (0.8-0.9)	*.04*
Allergenic foods at 3 mo		
1 y*	NA	NA
2 y*	NA	NA
3 y	0.81 (0.1-4.7)	.81
10 y	0.75 (0.1-4.2)	.75
Over first 10 y	0.34 (0.0-2.2)	.26
Allergenic foods by 6 mo		
1 y	0.62 (0.5-0.8)	*.002*
2 y	0.84 (0.6-1.3)	.41
3 y	0.70 (0.5-1.0)	*.05*
10 y	0.72 (0.50-1.0)	.07
Over first 10 y	0.70 (0.6-0.9)	*.005*
Allergenic foods by 9 mo		
1 y	0.81 (0.7-0.9)	*.03*
2 y	0.80 (0.6-1.03)	.09
3 y	0.78 (0.6-0.9)	*.04*
10 y	0.82 (0.7-1.0)	.08
Over first 10 y	0.84 (0.7-0.9)	*.02*
Allergenic foods by 12 mo		
1 y	0.68 (0.5-0.9)	*.004*
2 y	0.63 (0.4-0.9)	*.01*
3 y	0.63 (0.4-0.9)	*.006*
10 y	0.65 (0.5-0.9)	*.008*
Over first 10 y	0.68 (0.5-0.8)	*.0004*
Number of fruits and vegetables introduced by 3 mo		
1 y	0.98 (0.5-2.1)	.96
2 y	0.94 (0.3-2.7)	.91
3 y	1.37 (0.7-2.6)	.34
10 y	1.25 (0.7-2.4)	.50
Over first 10 y	1.00 (0.6-1.8)	1.00
Number of fruits and vegetables introduced by 6 mo		
1 y	0.74 (0.5-0.9)	*.04*
2 y	0.88 (0.6-1.3)	.56
3 y	0.70 (0.5-1.01)	.06
10 y	0.70 (0.5-0.9)	*.04*
Over first 10 y	0.75 (0.6-0.9)	*.02*
Number of fruits and vegetables introduced by 9 mo		
1 y	0.82 (0.6-0.9)	*.04*
2 y	0.88 (0.7-1.1)	.33
3 y	0.79 (0.6-0.9)	*.03*
10 y	0.80 (0.7-0.9)	*.03*
Over first 10 y	0.83 (0.7-0.9)	*.02*

CI, Confidence interval; *DD*, diet diversity; *OR*, odds ratio; *WHO*, World Health Organization.
Italicized text indicates statistical significance ($P < .05$).
*Data not shown as numbers did not converge.

positively correlated with FD at 6 and 9 months ($rs = 0.69, 0.64$ [$P < .0001$, $P < .0001$]), that is, increased intake of food allergens did not negatively impact on FD. Most interestingly, FAD at 12 months was significantly associated with a reduced odds of having FA at all time points.

Classifying DD according to number of fruits and vegetables introduced

As with FD and FAD, FVD at 3 months showed no association with any of the FA outcomes studied. However, FVD at 6 and 9 months reduced the odds of FA at 1, 10, and over the first 10 years of life. FVD at 6 months did not reduce the odds of having an FA at 2 or 3 years. FVD at 9 months did not reduce the odds of having an FA at 2 years but did at 3 years.

Using multivariate analysis (Table V), we showed that after correcting for significant factors, for each additional food introduced by 6 months using the WHO DD, the odds of developing FA was reduced by 21.6%, and for each additional food introduced (FD) by 9 months, the odds of developing FA over the first 10 years of life reduced by 9.8%. Similarly for each additional allergenic food (FAD) consumed (of 8) by 6 or 12 months, there was a significant reduction of 24.9% and 33.2%, respectively, in the likelihood of FA over the first 10 years of life. FVD at 6 and 9 months reduced the odds of developing an FA by 10 years by 23% and 16.9%, respectively.

In summary (Table VI and Figure 1), in the multivariate analysis, WHO DD was significantly associated with a reduced odds of FA at all time points, other than at 2 years. FD at 6 months was associated with reduced odds of FA at 1, 3, and over 10 years. FD at 9 months was associated with reduced FA at 2, 3, and 10 years. FAD at 6 months was associated with less FA at 1 and over 10 years. FAD at 9 months was only associated with less FA at 3 years. FAD at 12 months was associated with all reduced FA at all time points. FVD at 6 months was associated with less FA at 10 years and over 10 years. FVD at 9 months was

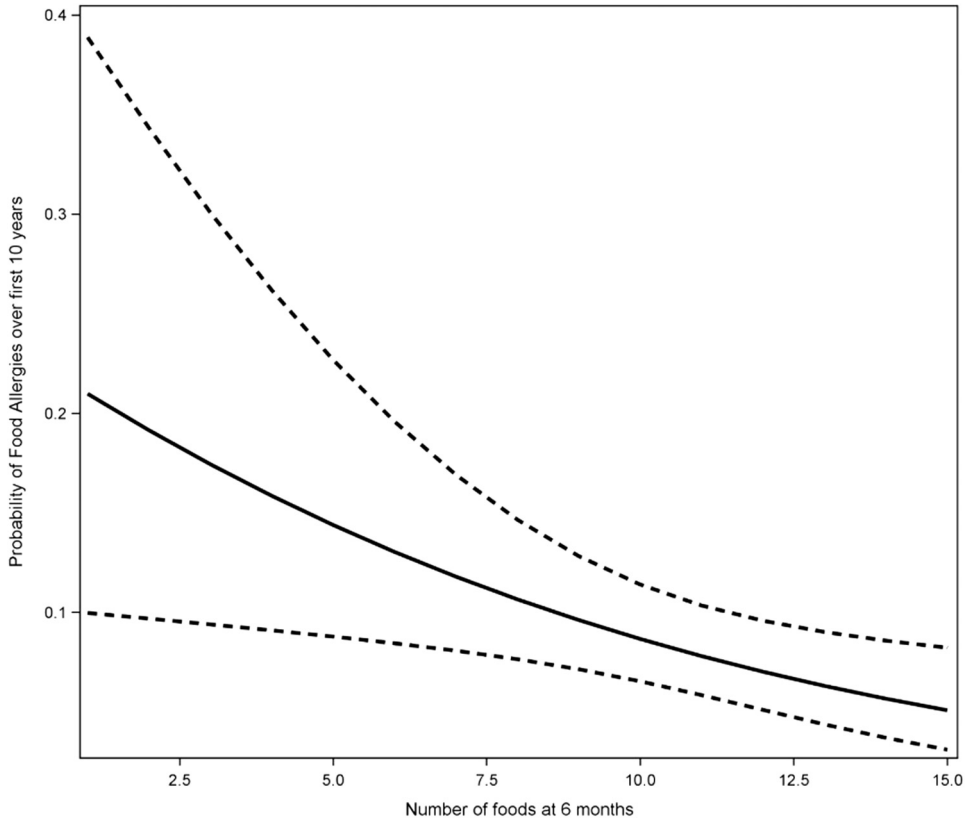


FIGURE 1. Food diversity at 6 months versus food allergy over 10 years. Multivariate analysis showed: food diversity at 6 months ($P = .0111$) significantly reduced the odds of food allergy over first 10 years (holding introduction of solids at the mean and having eczema ever = yes). Dotted line: 95% confidence interval. Solid line: *P* value.

associated with less FA at 3 and 10 years, and over the first 10 years of life.

Assessment of possible confounders

Association between eczema and age of introduction of solid foods. There does not appear to be an association between eczema and age of introduction of solid foods ($P = .57$). Children without eczema started solids on average at 14.93 (2.95) weeks versus those with eczema at 15.04 (2.61) weeks.

Association between diet diversity and eczema. Exploring the relationship between our 4 DD measures and eczema showed that only 1 variable, "number of allergic foods at 1 year," had an inverse association with eczema status ($P = .04$), but because the estimate for this variable only changed by 3.45%, this variable would not be considered a confounder leading to a reduced DD estimate.

Association between filaggrin loss-of-function outcomes and food allergy. We next explored the relationship between filaggrin haploinsufficiency and FA at years 1, 2, 3, 10, and over 10 years of age. Children having at least 1 FLG-LOF mutation were 4.2 times more likely to have FA at age 10 years than those children who did not have a filaggrin mutation (OR: 4.224, 95% CI: 1.474-12.106, $P = .007$).

Association between filaggrin loss-of-function outcomes and eczema. FLG-LOF did not show an association with eczema at age 2, 3, 10, and over 10 years. At 1 year the association was OR: 2.517, 95% CI: 1.005-6.308, $P = .0489$. However, there were only 34 children with FLG-LOF and eczema info at 1 year, 15 children at 2 years, 12 at 3 years, 35 at age 10, and 35 over the first 10 years of life, affecting the power of our statistical analysis.

Interaction between FA, DD, and eczema. We found no statistically significant interaction between FA, DD, and eczema (*P* values for the interaction term between = .13 and .92).

Interaction between food diversity and filaggrin loss-of-function outcomes and food allergy. Finally, we tested for an interaction between FD and FLG-LOF and FA; we found no significant interactions (*P* values for the interaction term between = .41 and .90). However, the number of children with FA who we had FLG-LOF mutations for was small in each age group. For example, in the 3-year-old age group (n = 286), there were only 33 who were filaggrin haploinsufficient, and there were only 15 who had FA, which resulted in very low power to detect significant differences.

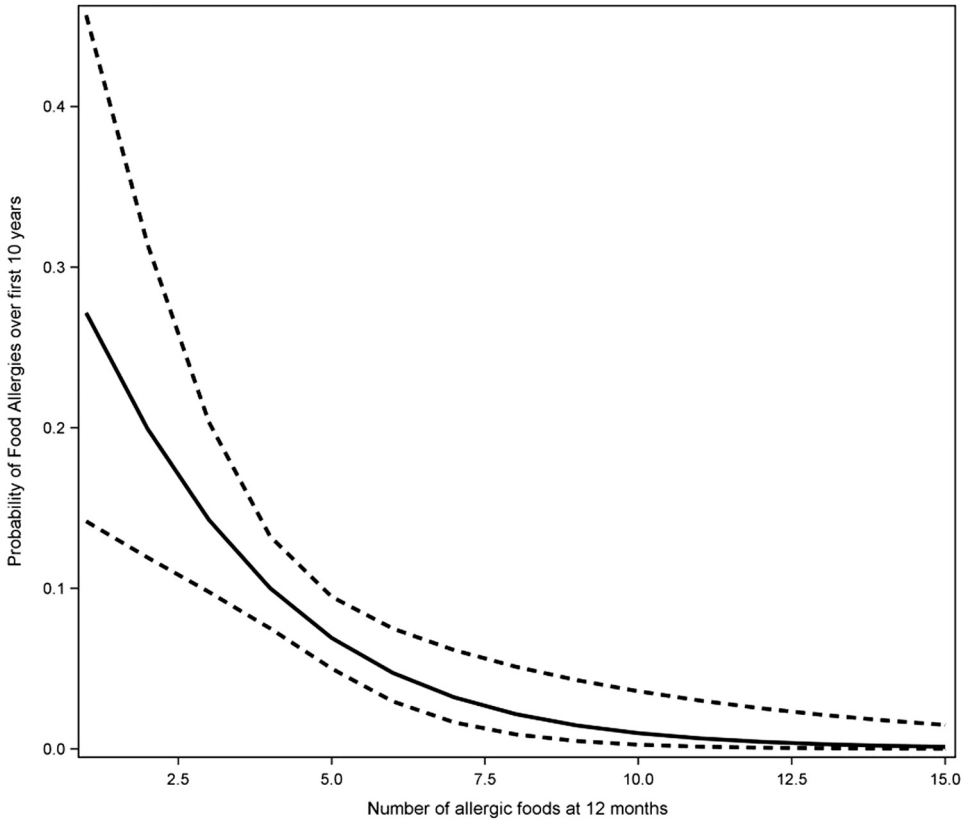


FIGURE 2. Food allergen diversity at 12 months versus food allergy over 10 years. Multivariate analysis showed: food allergen diversity at 12 months ($P = .0005$) significantly reduced the odds of food allergy over first 10 years (holding introduction of solids at the mean and having eczema ever = yes). Dotted line: 95% confidence interval. Solid line: *P* value.

DISCUSSION

In this study, we set out to determine if different measures of DD in the first year of life are associated with FA outcomes at 1, 2, 3, 10 years and over the first 10 years of life. We saw a consistent pattern of increased DD measured by the WHO definition, FD, FAD and FVD, and allergy outcomes. In particular, we have shown that for each additional food introduced by 6 months (FD), the odds of developing FA over the first 10 years of life was reduced by 10.8% even after correcting for other significant factors. Similarly, for each additional allergenic food consumed (FAD) by 1 year, there was a significant reduction of 33.2% in the likelihood of FA over the first 10 years of life. Filaggrin haploinsufficiency was associated with FA outcomes at 10 years of age and with eczema at 1 year. FAD did not negatively affect FD, which reassures us that an early and diverse intake of foods regarded as allergenic does not negatively impact on overall DD. Our data imply that there were no interactions or confounding seen between FA, DD, and eczema. We also tested the association between eczema and age of introduction of solid foods and did not find an association. Finally, we tested for an interaction among FD, FLG-LOF, and FA, and we found that none were statistically significant.

Our findings are in agreement with previous research. Roduit et al[3,14] reported an inverse association between DD in the first year of life and FA at 4 to 6 years. Hua et al[10] showed that increased FAD during the first year of life was associated with reduced sensitization to food and aeroallergens at 12 months, but no study has shown that FAD in early life reduces FA during the first decade of life. In accordance with Nwaru et al[15] and Hesselmar et al,[16] we did not find that having eczema affected age of introduction of solids. Eczema in the first year of life did not have an effect on DD either. Interestingly, we did not find any association between having a filaggrin mutation and any eczema over the first 10 years, in contrast to Flohr et al[17] and Ziyab et al,[18] though the associations reached significance at 1 year. However, this may represent a lack of power in the subset with genotype data.

Surprisingly, almost a quarter of infants had received solid foods by 3 months of age in our study. The reason for the introduction of solids at this early time point is the fact that the cohort was born in 2001-2002. At the time in the United Kingdom,[19] the recommendation was that solid food should be introduced to infants at approximately 4 months. This guideline was subsequently updated in 2003, when the UK Department of Health adopted the 2001 WHO's recommendations that complementary foods should be introduced at 6 months of age whilst continuing to breastfeed.

A limitation of our study and other previous studies mentioned is the lack of specifying the preparation of foods consumed (whether raw or cooked), or differentiation between homemade and commercially produced foods. Although we asked parents as part of our 6-month questionnaire whether they had introduced

TABLE V. Measures of diet diversity vs food allergy outcomes over the first 10 years of life using multivariate analysis, including only factors that have shown significance in the univariate analysis

Variable	Food allergy	OR (95% CI)	*P* value
WHO DD 6 mo*	1 y	0.68 (0.5-0.9)	*.002*
WHO DD 6 mo†	3 y	0.66 (0.5-0.8)	*.0003*
WHO DD‡	10 y	0.69 (0.5-0.9)	*.002*
WHO DD*	Over 10 y	0.78 (0.6-0.9)	*.02*
Number of foods by 6 mo*	1 y	0.86 (0.8-0.9)	*.008*
Number of foods by 6 mo†	3 y	0.84 (0.7-0.9)	*.006*
Number of foods by 6 mo‡	10 y	0.87 (0.8-0.9)	*.03*
Number of foods by 6 mo*	Over 10 y	0.89 (0.8-0.9)	*.01*
Number of foods by 9 mo§	2 y	0.78 (0.7-0.9)	*.009*
Number of foods by 9 mo‡	10 y	0.77 (0.6-0.9)	*.002*
Number of foods by 9 mo	3 y	0.97 (0.7-0.9)	*.005*
Number of foods by 9 mo*	Over 10 y	0.91 (0.8-1.0)	.14
Number of allergic foods by 6 mo*	1 y	0.68 (0.5-0.9)	*.02*
Number of allergic foods by 6 mo*	Over 10 y	0.75 (0.6-0.9)	*.02*
Number of allergic foods by 9 mo*	1 y	0.85 (0.7-1.0)	.09
Allergenic foods by 9 mo†	3 y	0.78 (0.6-0.9)	*.04*
Number of allergic foods by 9 mo*	Over 10 y	0.87 (0.7-1.01)	.07
Number of allergenic foods by 12 mo	1 y*	0.68 (0.5-0.9)	*.005*
	2 y§	0.64 (0.4-0.9)	*.02*
	3 y†	0.64 (0.4-0.9)	*.009*
	10 y‡	0.62 (0.4-0.9)	*.007*
	Over 10 y*	0.67 (0.5-0.8)	*.0005*
Number of fruits and vegetables by 6 mo*	1 y	0.77 (0.6-1.1)	.10
Number of fruits and vegetables by 6 mo‡	10 y	0.68 (0.5-0.9)	*.03*
Number of fruits and vegetables by 6 mo*	Over 10 y	0.77 (0.6-0.9)	*.04*
Number of fruits and vegetables by 9 mo*	1 y	0.83 (0.7-1.01)	.07
Number of fruits and vegetables by 9 mo†	3 y	0.79 (0.6-0.9)	.03
Number of fruits and vegetables by 9 mo‡	10 y	0.77 (0.6-0.9)	.02
Number of fruits and vegetables by 9 mo*	Over 10 y	0.83 (0.7-0.9)	.02

CI, Confidence interval; *DD*, diet diversity; *FA*, food allergy; *FLG-LOF*, filaggrin loss-of-function; *OR*, odds ratio; *WHO*, World Health Organization.
FLG-LOF at 10 years was associated with FA outcomes, but we did not include this in the multivariate model as the numbers were too small.
Italicized text indicates statistical significance ($P < .05$).
*Eczema and age of introduction of solid foods.
†Corrected for eczema.
‡Corrected for eczema, maternal food allergy, and parity.
§Corrected for eczema and maternal history of food allergy.

any packaged infant foods, we did not collect any further details. This is highly relevant as there is debate whether consumption of commercially produced infant food increases or decreases DD.[20,21] Furthermore, the microbial content is known to vary, with homemade infant meals having a higher aerobic colony count but lower pesticide count than those prepared commercially,[22] which potentially could influence gut microbiota. Research from our group has recently reported that commercially prepared infant food is consumed 15 times more frequently in young children consuming an exclusion diet for milk allergy.[23] Furthermore, data from a UK birth cohort suggest that a diet rich in fruit, vegetables, and home prepared foods, with only occasional use of commercially produced infant food, is associated with less FA at age 2 years.[24] Therefore, it is important that future DD research should explore this topic in more depth.

The most recent position statement regarding DD by the European Academy of Allergy and Clinical Immunology recommends that portion size and frequency of consumption should be measured when possible.[2] Typically observational cohort studies use food frequency questionnaire, a dietary assessment method that does not usually quantify the portion size of food consumed or whether the food was eaten singly or eaten as a minor ingredient in combination with other foods. In terms of our analysis, this does not allow us to differentiate the effect of eating substantial portions of specific foods, versus mere exposure to specific foods. Although using an FFQ in our study did not allow us to determine the significance of the portion size consumed, it is a practical method with low participant burden for collecting dietary data in a population at multiple time points. Other limitations are that data collected on maternal atopy and child eczema were reported, rather than diagnosed. As is the case for all observational cohort studies, the associations reported cannot determine causation. Finally, we wanted to test if infant DD modifies the penetrance of ethnically matched FLG-LOF mutations.[13,25,26] We were however limited by our sample size and were unable to find any significant associations.

The unique strengths of this study are FA outcome measures until 10 years, OFC-diagnosed FA, and a broader range of foods

TABLE VI. Summary of statistically significant association between diversity and food allergy outcomes

	At 1 y	At 2 y	At 3 y	At 10 y	Over 10 y
WHO diet diversity 6 mo	x		x	x	x
Food diversity 3 mo					
Food diversity 6 mo	x		x		x
Food diversity 9 mo		x	x	x	
Allergen diversity 3 mo					
Allergen diversity 6 mo	x				x
Allergen diversity 9 mo			x		
Allergen diversity 12 mo	x	x	x	x	x
Fruit and vegetable diversity 3 mo					
Fruit and vegetable diversity 6 mo				x	x
Fruit and vegetable diversity 9 mo			x	x	x

WHO, World Health Organization.

considered than previous studies. In addition, we have demonstrated an excellent retention of participants and have used prospectively collected data, thus limiting the impact of participant attrition and recall bias.[27] We have assessed DD using a variety of different definitions and arrived at the same conclusion, underscoring the robustness of the findings. If only 1 or 2 significant associations had been found, these associations could have been discounted as possibly being due to chance alone because of the multiple comparisons undertaken in the present analysis. However, there were many associations found between DD measures and FA outcomes that all showed consistent direction. We have accounted for confounding variables using adjusted multivariate regression models based on the methodologies of previous published studies.[3,9,28]

In conclusion, this study demonstrates that increased DD using 4 different measures in the first year of life is associated with reduced FA over the first 10 years of life, even after correcting for significant factors, particularly eczema. This reinforces the advice that a varied diet should be encouraged, unless otherwise indicated. Future research should ensure that a consistent approach is used to quantify DD, consider the method of preparation of complementary foods, and investigate the mechanisms involved.

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