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Increased food diversity in the first year of life is inversely associated with allergic outcomes in the second year

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Abstract

Background

The evidence on the relationship between diet diversity in early life and allergic outcomes was few and inconsistent. We sought to determine the association of food diversity in the first year of life with allergic outcomes in the second year.

Methods

Two thousand two hundred fifty-one mother-infant pairs from Tongji Maternal and Child Health Cohort (TMCHC) were involved in the study. Information on complementary foods introduction was obtained by telephone interview at 6- and 12-month postpartum follow-up. Any doctor-diagnosed allergic diseases in the second year were recorded at 2-year postpartum follow-up. Food allergies in infancy were assessed and self-reported by mothers at each postpartum follow-up. Multivariable logistic regression was used to examine the effect of food diversity at 6 and 12 months of age on later allergic diseases and food allergy.

Results

A total of 135 (6.0%) infants reported allergic diseases at between 1 and 2 years of age.

Independent of food allergy history of infants and other potential confounders, less food diversity at 6 months of age was associated with increased risk of later allergic diseases (OR 2.17, 95% CI 1.04–4.50 for 0 vs. 3–6 food groups). By 12 months of age, significant inverse associations with later allergic diseases (OR 2.35, 95% CI 1.03–5.32 for 1–5 vs. 8–11 food groups, and OR 1.98, 95% CI 1.16–3.37 for 6–7 vs. 8–11 food groups) and food allergy (OR 2.10, 95% CI 1.29–3.42 for 1–5 vs. 8–11 food groups) were observed. Children with higher food diversity in both periods had the lowest risk of allergic diseases during the second year of life.

Conclusions

A more diverse diet within the first year of life was associated with reduced risk of allergic diseases at 1–2 years of age. Introducing higher diversity of foods from 6 to 12 months of age might be an effective strategy to improve the allergy outcomes of infants in later life.

Key Message

Biodiversity hypothesis suggested that early exposure to diverse antigens from foods might be beneficial to the development of immune tolerance. Yet, the evidence on the association between food diversity in early life and the risk of allergic diseases is limited and the results were inconsistent. The present study showed an inverse association of food diversity at 6 and 12 months of age with doctor-diagnosed allergic diseases in the second year of life. The incidence of allergic diseases was the lowest among children with higher food diversity in both periods.

1 INTRODUCTION

Diet is an important environmental factor in early life, which influences the development of allergic diseases.^{1–4} Food diversity, defined as the number of different food groups consumed over a given period,⁵ may affect the development of immune tolerance via effect on the gut microbiome. Increased food diversity in infants during the complementary feeding period was associated with increased gut microbial diversity,⁶ which was related to reduced allergic sensitization and allergy outcomes in children.^{7–9} Emerging evidence indicated that early introduction of some foods such as peanut, eggs, or fish that were suggested to be avoided during infancy due to their allergenicity in past clinical practice guidelines¹⁰ might offer protection against later allergic disease and food allergy.^{3, 11, 12} Furthermore, early introduction of multiple allergenic foods by 6 months of age appeared achievable,¹³ and children introduced to a variety of foods and food allergens in the first year of life may have decreased risk of food allergy over the first decade of life.¹⁴ However,

thus far studies on the relationship between diet diversity in early life and the risk of allergy outcomes were few and the results were still inconsistent. Previous study reported no significant association between food diversity at age 6 months and the risk of eczema at 4 years of age.¹⁵ Yet, more recent evidences suggested that lower diet diversity in early life increased the risk of later allergic outcomes like atopic dermatitis,¹⁶ asthma,^{17, 18} allergic rhinitis,¹⁸ and atopic sensitization¹⁹ in infancy and childhood. In addition, little is known about the relationship between diet diversity in infancy and the risk of all allergies including asthma, eczema, allergic rhinitis, wheeze, allergic cough, urticarial, or other contact dermatitis.

The present study set out to investigate the association between food diversity at 6 and 12 months of age and the risk of all allergic outcomes during the second year of life through a prospective cohort study in Wuhan, China.

2 METHODS

2.1 Study design and participants

All study participants came from the Tongji Maternal and Child Health Cohort (TMCHC, registered at clinicaltrials.gov as NCT03099837), an ongoing, population-based prospective cohort study designed to examine the effect of maternal nutrition, lifestyle, and environmental factors on the health of mother-infant pairs. Pregnant women before 16 weeks of gestation were recruited at their first prenatal care visit in three research hospitals of Wuhan, China, between January 2013 and May 2016. Baseline characteristics of the participants were obtained at enrollment. They were followed up at their routine prenatal care during pregnancy and delivery hospitalization and then were approached by phone at 1, 3, 6, 12, and 24 months after delivery.

2.2 Ethical approval

All participants signed the informed consent at enrollment. The study was approved by the Ethics Review Committee of Tongji Medical College of Huazhong University of Science and Technology in China (NO. 201302 on 16 April 2013).

2.3 Infant feeding assessment

At around 1, 3, 6, and 12 months of age, mothers of infants were telephone interviewed by experienced interviewers to collect information on infant feeding practice in the past by using age-specific structured questionnaires. They were asked about breastfeeding, current feeding mode, age of infant formula introduction, age of breastfeeding cessation, use of dietary supplements, age of complementary foods introduction, type of complementary foods introduced, and food allergy history of infants at different ages. Mothers reported the food items that were given to the child in response to the question: "Has your child ever eaten the following food items from birth till now?" The complementary foods were

categorized into 6 food groups (cereals, vegetables, fruits, meats, fish, and eggs) at 6-month interview and 11 food groups (cereals, vegetables, fruits, meats, fish and seafoods, eggs, beans, peanut, other nuts, milk and milk products, and sweets) at 12 months interview. Food diversity was assessed by the number of food groups introduced.

Information obtained at different periods was combined to estimate any and full breastfeeding duration and the age of first complementary food introduction. Infants were categorized into “0 food groups,” “1–2 food groups,” and “3–6 food groups” at 6 months; and “1–5 food groups,” “6–7 food groups,” and “8–11 food groups” at 12 months according to their food diversity.

2.4 Allergic outcomes

Information about offspring allergic diseases diagnosed by doctors was self-reported by their mothers at 24-month postpartum follow-up. They were asked: “Has the infant seen a doctor because of any allergic diseases during the last year?” If “Yes,” the diagnosis and number of each allergic disease episodes were recorded.

Children were defined as having any allergic diseases when their mothers reported at least once that the child had doctor-diagnosed asthma, eczema, allergic rhinitis, wheeze, allergic cough, urticaria, or other contact dermatitis at 12–24 months of age. According to the definition of International Classification of Diseases (ICD)-11²⁰ of World Health Organization, allergic diseases were further categorized as two groups: (1) Allergic disease involving the respiratory tract included several clinically different conditions that can be considered as allergic disorders of the upper and lower respiratory tract, such as asthma, allergic rhinitis, wheeze, and allergic cough; (2) allergic disease involving skin included a heterogeneous group of disorders involving skin in which either allergy or hypersensitivity play a part, such as eczema, urticaria, and other contact dermatitis.

At 6-, 12-, and 24-month postpartum follow-up, mothers were asked about food allergy of infants. The question was: “Has your child ever had food allergies from birth till now?” If “Yes,” the type of allergic food and the age (in months) when the food allergies occurred were recorded to estimate the incidence of food allergies at the different ages.

2.5 Covariates

Basic information on maternal age (years), education level (<16, ≥16 schooling years), average personal income (<5,000, ≥5,000 Chinese yuan per month), nulliparity (Yes, No), allergic history (Yes, No), and smoking during pregnancy (Yes, No) was collected at enrollment. Pre-pregnancy body mass index (BMI, kg/m²) was calculated using self-reported pre-pregnancy weight (in kilograms) divided by the maternal height (in meters squared), which was measured at enrollment.

Information on the pregnancy outcomes of mother-infant pairs was obtained immediately

after delivery from the hospital notes, including gestational age at delivery (weeks), cesarean section (Yes, No), sex of child (boy, girl), birthweight (g), and season of birth. The season of birth was classified as spring (March-May), summer (June-August), autumn (September-November), and winter (December-February).

Full breastfeeding at 6 months of age was defined as breastfeeding, but water and tea without sugar were allowed and included exclusive and almost exclusive breastfeeding. Any breastfeeding at 12 months old was defined as receiving any breast milk, including full breastfeeding, breastfeeding plus infant formula, or other milk.

2.6 Statistical analysis

Descriptive statistics were summarized as mean $\pm$ SD for continuous variables and frequency (n) and percentages (%) for categorical variables. Differences of the background characteristics of mother-infant pairs were assessed by one-way analysis of variance (ANOVA) for continuous variables and chi-square test for categorical variables. Multivariable logistic regression was conducted to investigate the associations of food diversity by 6 and 12 months of age with the risk of allergic diseases and food allergy at subsequent year, and the results are presented as odds ratios (ORs) with 95% confidence intervals (CIs). Covariates that were associated with food diversity and allergic outcomes reported in the literature³ were chosen as potential confounders, including maternal age, pre-pregnancy BMI, parity, ethnicity, allergic history, cesarean section, gestational age at delivery, smoking during pregnancy, sex of child, birthweight, season of birth, and full breastfeeding at 6 months. Food allergy history of infants, which could affect infant feeding, were also adjusted in further analysis to exclude the reverse causality.

In order to assess the combined associations of food diversity both by 6 months and 12 months of age with the allergic outcomes during 1–2 years of age, children were divided into 4 categories as follows based on the diversity of foods at two periods: (1) LL: low food diversity at two periods (food groups ≤ 2 by 6 months and ≤ 7 by 12 months); (2) LH: low food diversity by 6 months and high food diversity by 12 months (food groups ≤ 2 by 6 months and food groups ≥ 8 by 12 months); (3) HL: high food diversity by 6 months and low food diversity by 12 months (food groups ≥ 3 by 6 months and food groups ≤ 7 by 12 months); and (4) HH: high food diversity at two periods (food groups ≥ 3 by 6 months and food groups ≥ 8 by 12 months). Multivariable logistic regression was performed to calculate the ORs (95% CIs) of allergic outcome adjustment for potential confounders.

Stratified analysis was performed to explore the potential modification effect including delivery mode, infants feeding practice, age of complementary food introduction, and food allergy history of infants on the allergic outcomes.

All the statistical analyses were performed using SAS 9.4 software (Statistics Analysis System, USA), and $p < .05$ was considered statistically significant.

3 RESULTS

A total of 2,266 singleton live-born infants were approached at each follow-up at ages 6, 12, and 24 months. After excluding those introduced complementary food prior to 4 months of age ($n = 15$), 2251 were involved in the final analysis. The background characteristics were similar for the participants included in the present study compared with those who were followed up at least once from 6 up to 24 months of age (Table [S1](#)).

Among the 2251 children, 135(6.0%) infants were diagnosed with allergic diseases during the second year of life. Among them, allergic rhinitis was the most and accounted for 41%, while allergic cough was the least which accounted for 2% of the allergic diseases. Over 80% infants received complementary feeding at age 5 and 6 months. The food diversity at 6 months ranged from 0 to 6 groups, and 44.0% infants were categorized into highest food groups (3–6). By the age of 12 months, the food diversity was from 1 to 11 groups, and 48.1% infants were categorized into highest food groups of 8–11. Table [1](#) shows the background characteristics of the participants according to the categories of food groups by 6 months and 12 months, respectively. Children with higher birthweight and those with higher average personal income were more likely to be introduced more diverse food at 6 months of age. Children of mothers with higher education level and nulliparity, infants delivered vaginally and exclusively breastfed until 6 months of age, were more likely to have a higher diversity of foods at 12 months of age. Children with food allergy history and those introduced complementary food later were more likely to have a lower diversity of foods in the first year of life. No statistically significant difference in the risk of allergic diseases and food allergy was observed among infants starting complementary feeding at 4, 5, 6 months, and later (Table [S2](#)).

TABLE 1. Demographics characteristics of the study population according to food diversity during the first year of life

Characteristics	Overall	Food diversity by 6 months of age				Food diversity by 12 months of age	
		0 food group	1–2 food groups	3–6 food groups	<i>p</i>	1–5 food groups	6–7 food groups
<i>N</i>	2251	101	1160	990		170	999
Mothers							
Ethnicity (Han Chinese)	2199 (97.7)	100 (99.0)	1143 (98.5)	956 (96.6)	.007	167 (98.2)	979 (98.0)
Maternal age, year	28.3 ± 3.4	28.2 ± 3.5	28.3 ± 3.5	28.2 ± 3.4	.664	28.5 ± 3.6	28.4 ± 3.5

Characteristics	Overall	Food diversity by 6 months of age				Food diversity by 12 months of age	
		0 food group	1–2 food groups	3–6 food groups	<i>p</i>	1–5 food groups	6–7 food groups
Pre-pregnancy BMI, kg/m ²	21.0 ± 2.8	20.8 ± 2.6	21.0 ± 2.6	21.0 ± 2.9	.793	21.2 ± 2.8	21.0 ± 2.8
Education (≥16 schooling years)	1285 (57.1)	49 (48.5)	649 (56.0)	587 (59.3)	.061	80 (47.1)	567 (56.8)

Note

Data are expressed as mean ± SD or *n* (%).
Abbreviations: BMI, body mass index; CNY, Chinese Yuan, 1 CNY ≈ 0.16US\$.

At 6 months of age, cereals were the most introduced food groups, followed by fruits, egg yolk, and vegetables. Infants introduced more food groups were more likely to be introduced cereals, fruits, eggs, and vegetables too (Table S3). By the age of 12 months, almost all of infants were introduced cereals, vegetables, fruits, eggs, and meats, while peanut and other nuts were less introduced (Table S4).

The unadjusted and adjusted associations of food diversity by 6 and 12 months of age with the risk of allergic outcomes occurring during the second year of life are shown in Table 2. Compared to children introduced 3–6 food groups by 6 months of age, those not introduced to any complementary foods had an increased risk of allergic diseases, especially allergic disease involving skin during their second year of life in unadjusted model and adjusted model I. Further adjusted for food allergy history of infants, the risk for allergic diseases (OR 2.17, 95% CI 1.04–4.54) and allergic disease involving skin (OR 3.17, 95% CI 1.23–8.15) remained stable. By 12 months of age, significant inverse dose-response relationships with later allergic diseases, especially with allergic disease involving the respiratory tract, were observed after adjusted for food allergy history of infants and other potential confounders. Food diversity by 6 months of age was not associated with the risk of food allergy at 1–2 years of age in infancy. However, less food groups introduced by 12 months of age were associated with increased risk of later food allergy in infancy, and the relationship remained stable after adjusted the food allergy history of infants and other potential confounders (OR, 95%CI) for 1–5 food groups vs. 8–11 food groups (2.10, 1.29–3.42).

TABLE 2. Associations of food diversity by 6 and 12 months of age with the risk of allergic outcomes during 1–2 years of age (*n* = 2,251)

Allergic outcomes	Food diversity by 6 months of age			Food diversity by 12 months of age		
	0 food group	1–2 food groups	3–6 food groups	1–5 food groups	6–7 food groups	8–11 food groups
Allergic disease						
<i>N</i> (%)	10 (9.9)	77 (6.6)	48 (4.9)	15 (8.8)	72 (7.2)	48 (4.4)
Unadjusted model	2.16 (1.06–4.41)	1.40 (0.96–2.02)	1	2.09 (1.14–3.81)	1.67 (1.15–2.44)	1
Adjusted model I ^a	2.19 (1.06–4.54)	1.43 (0.98–2.08)	1	2.05 (1.11–3.79)	1.68 (1.15–2.45)	1
Adjusted model II ^b	2.17 (1.04–4.50)	1.42 (0.98–2.07)	1	1.87 (1.01–3.48)	1.64 (1.12–2.40)	1
Allergic disease involving the respiratory tract						
<i>N</i> (%)	4 (4.0)	42 (3.6)	26 (2.6)	9 (5.3)	41 (4.1)	22 (2.0)
Unadjusted model	1.53 (0.52–4.47)	1.39 (0.85–2.29)	1	2.69 (1.22–5.59)	2.06 (1.22–3.49)	1
Adjusted model I ^a	1.28 (0.42–3.83)	1.38 (0.83–2.27)	1	2.50 (1.11–5.63)	2.01 (1.18–3.43)	1
Adjusted model II ^b	1.28 (0.42–3.83)	1.38 (0.83–2.27)	1	2.35 (1.01–5.48)	1.98 (1.12–3.40)	1

Note

Data were shown as *N* (%) or OR (95% CI).

^a Model I adjusted for maternal age, pre-pregnancy BMI, parity, ethnicity, allergic history, education, average personal income, cesarean section, gestational age at delivery, smoking during pregnancy, fetal gender, birthweight, season of birth, and full breastfeeding at 6 months of age.

^b Model II adjusted for variables in model I and food allergy history of infants by 6 months of age when assessed the effect of food diversity at 6 months of age on allergic outcomes, and adjusted for model I and food allergy history of infants by 12 months of age when assessed the effect of food diversity at 12 months of age on allergic outcomes.

When food diversity was considered as a continuous predictor in adjusted model, the result showed that the risk of allergic diseases during the second year significantly reduced 15% with each additional food groups introduced by 6 months of age (OR 0.85, 95% CI 0.73–1.00). For each additional food groups introduced by 12 months of age, there was a significant reduction of 15% in the risk of later allergic diseases (OR 0.85, 95% CI 0.75–0.95) and 12% in

the risk of later food allergy (OR 0.88, 95% CI 0.79–0.98) (data are shown in Table 3).

TABLE 3. Associations of food diversity as a continuous predictor by 6 and 12 months of age with the risk of allergic outcomes during 1–2 years of age ($n = 2,251$)

Allergic outcomes	<i>N</i> (%)	Food diversity by 6 months of age, continuous model	Food diversity by 12 months of age, continuous model
Allergic disease	135 (6.0)		
Unadjusted model		0.86 (0.73–1.00)	0.83 (0.74–0.94)
Adjusted model I ^a		0.85 (0.73–1.00)	0.83 (0.74–0.94)
Adjusted model II ^b		0.85 (0.73–1.00)	0.85 (0.75–0.95)
Allergic disease involving the respiratory tract	72 (3.2)		
Unadjusted model		0.96 (0.78–1.18)	0.79 (0.68–0.92)
Adjusted model I ^a		0.99 (0.79–1.22)	0.79 (0.68–0.93)
Adjusted model II ^b		0.99 (0.79–1.22)	0.80 (0.69–0.94)
Allergic disease involving skin	66 (2.9)		
Unadjusted model		0.80 (0.64–0.99)	0.89 (0.75–1.05)
Adjusted model I ^a		0.76 (0.61–0.95)	0.88 (0.74–1.04)
Adjusted model II ^b		0.76 (0.61–0.96)	0.89 (0.75–1.07)
Food allergy	227		

Note

Data were shown as *N* (%) or OR (95% CI).

^a Model I adjusted for maternal age, pre-pregnancy BMI, parity, ethnicity, allergic history, education, average personal income, cesarean section, gestational age at delivery, smoking during pregnancy, fetal gender, birth weight, season of birth, and full breastfeeding at 6 months of age.

^b Model II adjusted for variables in model I and food allergy history of infants by 6 months of age when assessed the effect of food diversity at 6 months of age on allergic outcomes, and adjusted for model I and food allergy history of infants by 12 months of age when assessed the effect of food diversity at 12 months of age on allergic outcomes.

The combined associations of food diversity by 6 and 12 months of age with later allergic outcomes are shown in Table 4. Compared to infants with higher diversity of foods in both periods, those with lower diversity of foods in any period had an increased risk of later allergic diseases, including both allergic diseases involving the respiratory tract and allergic disease involving skin. Stratified analyses were performed to assess the potential effect modification including delivery mode, infants feeding practice, age of complementary food introduction, and food allergy history of infants on the association between food diversity and allergic outcomes at subsequent year. The association of lower food diversity with increased risk of subsequent allergic diseases remained unchanged at different subgroups (Table S5).

TABLE 4. Combined associations of food diversity both by 6 and 12 months of age with the allergic outcomes during 1–2 years of age (*n* = 2251)

Allergic outcomes	Food diversity by 6 and 12 months of age			
	LL	LH	HL	HH
Allergic disease				
<i>N</i> (%)	50 (6.9)	37 (6.9)	37 (8.3)	11 (2.0)
Unadjusted model	3.60 (1.86–6.99)	3.61 (1.82–7.15)	4.42 (2.23–8.77)	1
Adjusted model I ^a	3.65 (1.87–7.12)	3.76 (1.89–7.49)	4.47 (2.24–8.91)	1
Adjusted model II ^b	3.49 (1.79–6.82)	3.76 (1.88–7.49)	4.39 (2.20–8.75)	1
Allergic disease involving the respiratory tract				
<i>N</i> (%)	28 (3.9)	18 (3.4)	22 (5.0)	4 (0.7)
Unadjusted model	5.44 (1.90–15.6)	4.71 (1.58–14.00)	7.06 (2.42–20.65)	1
Adjusted model I ^a	5.15 (1.78–14.88)	4.76 (1.59–14.26)	7.00 (2.38–20.63)	1
Adjusted model II ^b	4.96 (1.72–14.36)	4.76 (1.59–14.26)	6.91 (2.35–20.38)	1
Allergic disease involving skin				
<i>N</i> (%)	23 (3.2)	19 (3.5)	17 (3.8)	7 (1.3)
Unadjusted model	2.52 (1.07–5.92)	2.83 (1.18–6.78)	3.06 (1.26–7.46)	1
Adjusted model I ^a	2.78 (1.17–6.59)	3.10 (1.28–7.51)	3.17 (1.29–7.79)	1

Note

Data were shown as *N* (%) or OR (95% CI). AD: allergic disease; AD-RT: allergic disease involving the respiratory tract;

AD-S: allergic disease involving skin. LL: introduced ≤ 2 food groups by 6 months of age and ≤ 7 food groups by 12 months of age; LH: introduced ≤ 2 food groups by 6 months of age and ≥ 8 food groups by 12 months of age; HL: introduced ≥ 3 food groups by 6 months of age and ≤ 7 food groups by 12 months of age; HH: introduced ≥ 3 food groups by 6 months of age and ≥ 8 food groups by 12 months of age.

^a Model I adjusted for maternal age, pre-pregnancy BMI, parity, ethnicity, allergic history, education, average personal income, cesarean section, gestational age at delivery, smoking during pregnancy, fetal gender, birth weight, season of birth, and full breastfeeding at 6 months of age.

^b Model II adjusted for variables in model I and food allergy history of infants by 12 months of age.

4 DISCUSSION

In the current study, most of the infants received complementary feeding start at age 5 and 6 months. The starting age of complementary feeding was not associated with the risk of allergic diseases in their second year of life among those introduced the first complementary food after 4 months of age. Lower food diversity by age 6 months was associated with increased risk of later allergic diseases, especially allergic disease involving skin. By the age of 12 months, the food diversity was inversely related to later allergic diseases and food allergy in a dose-response manner. Children with more diverse foods in both periods had the lowest risk of allergic diseases during the second year of life and the results of stratified analysis were broadly consistent.

Previous evidence suggested there was no significant association between food diversity at age 6 months and the risk of eczema at 4 years of age.¹⁵ However, the other evidence showed that early complementary feeding might play an important role in the development of allergic diseases later in childhood.¹⁶⁻¹⁹ Data from the Protection Against Allergy Study in Rural Environments (PASTURE) cohort suggested that an increased diversity of food introduction within the first year of life was associated with reduced risk of atopic dermatitis during 1–4 years of age.¹⁶ The PASTURE study also showed that an increased food diversity from 3 to 12 months of age was associated with decreased risk of asthma and sensitization to food allergens up to 6 years of age.¹⁷ The other study involving 3142 children from Finnish birth cohort reported the protective effect of food diversity within the first 6 and 12 months on the development of atopic asthma and allergic rhinitis by 5 years of age.¹⁸ Our results complement this evidence base by showing that more diverse foods introduced within the first year of life may protect against allergic diseases and food allergy during 1–2 years of age, and support the hypothesis that early exposure to diverse antigens from foods might be beneficial to the development of immune tolerance.²¹ In addition, introducing more diverse complementary food at as early as 6 months of age and adherence to more diverse diet later was associated with the lowest risk of later allergic diseases, including allergic disease involving the respiratory tract and allergic disease involving skin, meaning that introducing higher diversity of foods within the first year of life might be an effective strategy for protection against the development of later allergic

diseases.

Evidence is emerging that babies born by cesarean section had an increased likelihood of allergic diseases, and the potential biological mechanisms are that infants born by cesarean section had a reduced exposure to the maternal microbiota compared to vaginal birth, which affected the development and differentiation of infants' immune system.²² Previous evidence also suggested that breastfeeding had a protective effect against allergic diseases.^{23, 24} In the present study, stratified analyses showed similar effect of food diversity on allergic outcomes in subgroups, cesarean section, and full breastfeeding did not modify the associations between food diversity within the first year of life and later allergic outcomes. Our results showed that children with food allergy history and those introduced to complementary food later had a lower food diversity within the first year of life. When the analyses were evaluated in infancy stratified by food allergy history of infants and the age of complementary food introduction, the inverse associations of food diversity between 6 months and 12 months of age and allergic diseases remained stable in subgroups. The results highlight the important role of food diversity for infants, and clinicians should reinforce the guidance of diverse diet in the complementary feeding period to prevent allergic diseases in later life.

Our study has several strengths and limitations. To our knowledge, participants in previous studies are generalizable to Western population. Our study provided valuable evidence into the beneficial effect of food diversity within the first year of life on the development of allergic diseases among Chinese. Secondly, the prospective design and collection of data on food diversity at 6 and 12 months of age minimized the recall bias. Focusing the analyses on allergic outcomes occurring after the assessment of food diversity allowed us to avoid the reverse causality effect. We also assessed the effect of constant exposure to diverse food antigens from 6 to 12 months of age on later allergic outcomes, and the results highlight the important role of food diversity in complementary feeding period. In addition, our study adjusted for food allergy history of infants, which may affect the diversity of food and induce a reverse causality effect. A limitation of the present study is that the definition of allergic diseases based on the reported doctor's diagnosis by mothers may result in an underestimation of the prevalence, which may weaken the relationship of the diversity of food with allergic diseases; however, a significant association was still found. Another limitation is that we did not measure the gut microbiome of these infants, which limits the assessment of the potential modification effects of food diversity on the development of allergic diseases by microbial factors.

5 CONCLUSIONS

In summary, a more diverse diet within the first year of life was associated with reduced risk of allergy diseases at 1–2 years of age. Introducing higher diversity of foods from 6 to 12 months of age might be an effective strategy to prevent allergy diseases of infants in later life.

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CONFLICT OF INTEREST

The authors report no conflict of interest. The authors do not have any financial, personal, political, intellectual, or religious interests to disclose.

AUTHOR CONTRIBUTIONS

Chunrong Zhong: Conceptualization (lead); Data curation (lead); Investigation (lead); Methodology (lead); Writing – original draft (lead). **Jinrong Guo:** Conceptualization (equal); Data curation (equal); Investigation (equal). **Tianqi Tan:** Data curation (equal); Investigation (equal). **Huanzhuo Wang:** Data curation (equal); Investigation (equal). **Lixia Lin:** Data curation (equal); Investigation (equal). **Duan Gao:** Data curation (equal); Investigation (equal). **Qian Li:** Data curation (equal); Investigation (equal). **Guoqiang Sun:** Supervision (equal). **Guoping Xiong:** Supervision (equal). **Xuefeng Yang:** Supervision (equal). **Liping Hao:** Supervision (equal). **Hongying Yang:** Supervision (equal). **Nianhong Yang:** Funding acquisition (lead); Project administration (lead); Writing – review & editing (lead).

Supporting Information



Filename	Description
pai13707-sup-0001-TableS1-S5.docx Word 2007 document , 32.9 KB	Table S1-S5

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Table S1. Characteristics of all subjects followed up at least once during 6-24 months of age and participants in the present study

Characteristics	All subjects (n=5228)	Study subjects (n=2251)	<i>P</i>
Mothers			
Ethnicity (Han Chinese)	5095(97.5)	2199(97.7)	0.550
Maternal age, y	28.3±3.5	28.3±3.4	0.864
Pre-pregnancy BMI, kg/m ²	20.9±2.8	21.0±2.8	0.057
Education (≥ 16 schooling years)	2943(56.3)	1285(57.1)	0.525
Average personal income (≥5000 CNY)	3140(60.1)	1399(62.2)	0.236
Nulliparity (Yes)	4378(83.7)	1887(83.8)	0.924
Smoking during early pregnancy (Yes)	416(8.0)	177(7.9)	0.890
Allergic history (Yes)	440(8.4)	206(9.2)	0.299
Gestational age at delivery, wk	39.1±1.4	39.2±1.4	0.451
Cesarean section (Yes)	2295(43.9)	933(41.5)	0.050
Infants			
Sex (boy)	2821(54.0)	1220(54.2)	0.887
Birth weight, g	3342±438	3334±434	0.447
Season at birth			
Spring (March-May)	1185(22.7)	544(24.2)	0.200
Summer (June-August)	1279(24.5)	573(25.5)	
Autumn (September-November)	1811(34.6)	728(32.3)	
Winter (December-February)	953(18.2)	406(18.0)	
Full breastfeeding at 6 months (Yes)	2410(57.9)	1295(57.5)	0.838
Any breastfeeding at 12 months (Yes)	1378(32.4)	763(33.9)	0.229
Age of complementary food introduction, months	5.5±0.6	5.5±0.6	0.207

Data are expressed as mean ± SD or n (%). BMI, body mass index; CNY, Chinese Yuan, 1 CNY ≈0.16US\$.

Table S2. Prevalence of allergic outcomes and food allergies by time point of first complementary food introduction

Allergic outcomes	N(%)	Age of complementary food introduction				<i>P</i>
		4 months (n=348)	5 months (n=993)	6 months (n=809)	Not introduced (n=101)	
Allergic disease	135(6.0)	22(6.3)	53(5.3)	50(6.2)	10(9.9)	0.307
Allergic disease involving the respiratory tract	72(3.2)	16(4.6)	32(3.2)	20(2.5)	4(4.0)	0.287
Allergic disease involving skin	66(2.9)	8(2.1)	27(2.6)	31(3.8)	6(5.9)	0.054
Food allergy by the age of 6 months	312(13.9)	55(15.8)	153(15.4)	104(12.9)	-	0.235
Food allergy by the age of 12 months	613(27.2)	95(27.3)	270(27.2)	205(25.8)	39(38.6)	0.060
Food allergy by the age of 24 months	227(11.3)	31(10.1)	90(10.2)	97(13.3)	9(10.1)	0.195

Table S3. The kinds of complementary foods according to food diversity at age of 6 months

Complementary foods	Overall (n=2251)	Food diversity at age of 6 months			<i>P</i>
		0 food groups (n=101)	1-2 food groups (n=1160)	3-6 food groups (n=990)	
Cereals	2113(93.9)	0(0)	1126(97.1)	987(99.7)	<0.001
Vegetables	771(34.4)	0(0)	138(12.0)	633(63.9)	<0.001
Fruits	1299(58.1)	0(0)	370(31.9)	929(93.8)	<0.001
Meats	36(1.6)	0(0)	1(0.1)	35(3.5)	<0.001
Fish & seafoods	45(2.1)	0(0)	1(0.1)	44(4.4)	<0.001
Egg yolk	898(39.8)	0(0)	203(17.5)	687(69.4)	<0.001

Table S4. The kinds of complementary foods according to food diversity at age of 12 months

Complementary foods	Overall (n=2251)	Food diversity at age of 12 month			<i>P</i>
		1-5 food groups (n=170)	6-7 food groups (n=999)	8-11 food groups (n=1082)	
Cereals	2246(99.8)	165(97.6)	999(100)	1182(100)	<0.001
vegetables	2197(97.6)	133(78.2)	984(98.5)	1080(99.8)	<0.001
Fruits	2196(97.6)	136(80.0)	981(98.2)	1079(99.7)	<0.001
Meats	2032(90.3)	66(38.8)	906(90.7)	1060(98.0)	<0.001
Fish & seafoods	1910(84.9)	40(23.5)	817(81.8)	1053(97.3)	<0.001
Eggs	2056(91.3)	85(50.0)	906(90.7)	1065(98.4)	<0.001
Milk & milk products	726(32.3)	11(6.5)	107(10.7)	608(56.2)	<0.001
Beans	881(39.1)	4(2.4)	144(14.4)	733(67.7)	<0.001
Peanut	313(13.9)	1(0.6)	31(3.1)	281(26.0)	<0.001
Other nuts	83(3.7)	0(0)	5(0.5)	78(7.2)	<0.001
Sweets	1975(87.7)	100(58.8)	829(83.0)	1046(96.7)	<0.001

Table S5. Stratified analyses: potential effect modification for the impact of during 6 months and 12 months of age on any allergy diseases at subsequent year.

Stratification factors	N	LL		LH		HL		HH	
		Allergy diseases N(%)	Adjusted OR [†] (95%CI)	Allergy diseases N(%)	Adjusted OR [†] (95%CI)	Allergy diseases N(%)	Adjusted OR [†] (95%CI)	Allergy diseases N(%)	Adjusted OR [†] (95%CI)
Delivery mode									
Vaginal birth	1318	24(6.1)	2.73(1.20-6.19)	23(7.0)	3.23(1.41-7.38)	19(7.4)	3.43(1.47-8.03)	8(2.4)	1
Cesarean section	933	26(7.9)	5.50(1.63-18.50)	14(6.8)	5.08(1.43-18.05)	18(9.6)	6.96(2.01-24.18)	3(1.4)	1
Full breastfeeding by 6 months of age									
Yes	1295	25(6.3)	2.96(1.25-6.98)	23(6.7)	3.38(1.42-8.03)	19(8.2)	4.10(1.68-10.00)	7(2.2)	1
No	956	25(7.6)	4.41(1.50-12.95)	14(7.4)	4.44(1.43-13.81)	18(8.5)	4.99(1.65-15.12)	4(1.8)	1
Age of complementary food introduction [‡]									
4-5 months	1341	28(7.4)	3.19(1.43-7.12)	19(6.5)	3.38(1.47-7.76)	28(8.5)	4.19(1.94-9.06)	9(2.1)	1
6.0 months	809	22(6.3)	3.82(0.87-16.73)	18(7.4)	5.41(1.22-23.91)	9(7.9)	5.46(1.14-26.17)	2(1.7)	1
Food allergy history of infants by 12 months of age									
Yes	613	20(8.3)	6.12(1.40-26.79)	14(11.0)	8.16(1.80-36.95)	14(11.4)	8.32(1.84-37.65)	2(1.6)	1
No	1638	30(6.2)	2.96(1.38-6.33)	23(5.6)	2.82(1.28-6.20)	23(7.2)	3.51(1.60-7.75)	9(2.1)	1

LL: introduced ≤ 2 food groups by 6 months of age and ≤ 7 food groups by 12 months of age; LH: introduced ≤ 2 food groups by 6 months of age and ≥ 8 food groups by 12 months of age; HL: introduced ≥ 3 food groups by 6 months of age and ≤ 7 food groups by 12 months of age; HH: introduced ≥ 3 food groups by 6 months of age and ≥ 8 food groups by 12 months of age.

[†]All covariates are as follow: maternal age, pre-pregnancy BMI, parity, ethnicity, allergic history, education, average personal income, cesarean section, gestational age at delivery, smoking during pregnancy, fetal gender, birth weight, season of birth, timing of food introduction, full breastfeeding at 6 months of age, and food allergy history of infants by 12 months of age. Each of the subgroups were adjusted for all covariates except itself.

[‡] The sample of children who were not introduced any complementary foods till 6 months interview (n=101) was too small to analyses and was excluded in the stratified analyses.