

Letter to the Editor

Growth and nutrition in children with food allergy requiring amino acid–based nutritional formulas*To the Editor:*

Although children with food allergy are at risk for nutritional deficiencies, studies investigating nutrition and growth in children with extensive dietary restrictions are limited. Amino acid–based formulas, which are often necessary for children who avoid multiple food allergens,¹ are designed to be nutritionally complete and can be effective treatment for children with eosinophilic gastrointestinal disease (EGID).^{2,3} Although a small number of studies have described features of growth, nutrition, or both in patients with food allergy,⁴⁻⁶ none have specifically investigated those whose dietary restrictions necessitate amino acid–based formula supplementation.

This cross-sectional study investigated macronutrient intake, growth, and select micronutrient adequacy in children with multiple food allergies who require formula supplementation. We also investigated the risk for choline deficiency, which has been observed in children requiring parenteral nutritional support,⁷ can manifest as hepatic dysfunction (in severe cases), and could be a potential problem in children avoiding choline-rich foods, such as dairy, egg, and nuts.⁸ Children were invited to participate if they were between the ages of 6 months and 17 years, had physician-diagnosed food allergy (based on clinical history, food-specific IgE levels, skin prick test responses, and/or food challenge results), were treated with an elimination diet, and required an amino acid–based formula to satisfy some/all of their daily nutritional needs. Children with a history of renal, hepatic, or mitochondrial disease; malabsorption disorders; or recent illness were excluded. Thirty-two of 81 potential participants agreed to participate in the 1-day visit; all had complete health and growth assessments, whereas the laboratory and dietary intake assessments were completed in 31 and 27 participants, respectively. The Johns Hopkins Institutional Review Board approved the study protocol.

All children had a complete physical examination, including SCORAD index for eczema,⁹ weight/height measurements, and review of their medical history, including medication, vitamin/supplement, and systemic corticosteroid use in the past year. Families met with a research dietitian to review dietary history, current intake, and instructions to complete a 3-day food record. Food records were analyzed by using the Nutrition Data System for Research to estimate average daily nutrient intake values, which were then compared with dietary reference intake values.¹⁰ Laboratory testing included measurements of albumin, calcium, hemoglobin, iron, phosphate, vitamin B12, folate (serum), aspartate transaminase, alanine transaminase, creatine phosphokinase, and plasma choline levels (with *z* scores calculated from the percentiles described by Guerrero et al⁷).

Data from the National Health and Nutrition Examination Survey 2007-2010 (NHANES 2007-2010) were used for comparison of study participants' growth measurements. Age-adjusted weight, height, and body mass index (BMI) and weight-for-height percentiles were calculated by using the US Centers for Disease Control and Prevention (CDC)'s Epi Info software (version 3.5.4, July 23, 2008), as described in the [Methods](#)

TABLE I. Study population

	Study participants (n = 32)	NHANES 2007-2010 (n = 6334) [†]
Male sex, % (no.)*	78.1 (25)	50.9
Age (y), mean (SE)*	5.7 (0.8)	8.4
Age (y), median (range)	4.1 (0.8-15.8)	7.3
Race/ethnicity, % (no.)*		
White	53.1 (17)	56.3
Black	6.3 (2)	13.9
Hispanic	3.1 (1)	22.0
Other	37.5 (12)	7.9
Major allergens avoided, % (no.)		
Milk	87.5 (28)	
Egg	81.3 (26)	
Wheat	59.4 (19)	
Soy	81.3 (26)	
Peanut	87.5 (28)	
All 5 major allergens, total daily energy intake from formula, % (no.)	56.3 (18)	
>75% Calories/formula	23.1 (6)	
51% to 75% Calories/formula	19.2 (5)	
25% to 50% Calories/formula	46.2 (12)	
<25% Calories/formula	11.5 (3)	
Formula type, % (no.)		
EleCare (Abbott Nutrition, Columbus, Ohio)	65.6 (10)	
Neocate (Nutricia, Gaithersburg, Md)	34.4 (11)	
Neocate (E028) Splash (Abbott Nutrition)	28.1 (9)	
Nutramigen AA (Mead Johnson, Glenview, Ill)	3.1 (1)	
Multiple	3.1 (1)	
Comorbid conditions, % (no.)		
Asthma	46.9 (15)	
Atopic dermatitis	53.1 (17)	
Mean SCORAD score (range) [‡]	7.7 (0-77)	
Rhinitis	40.6 (13)	
Eosinophilic esophagitis	40.6 (13)	
Eosinophilic enteropathy	3.1 (1)	
Food allergy, % (no.)		
IgE mediated	25.0 (8)	
Non-IgE mediated	46.9 (15)	
Mixed	28.1 (9)	
Gastrostomy tube, % (no.)	9.4 (3)	
Taking other supplements/MVI, % (no.)	40.6 (13)	
Subjects with systemic steroid exposure in past year, % (no.)	46.9 (15)	
Median steroid, d/y (range) [§]	10 (2-42)	

MVI, Multivitamin.

**P* < .005, comparison of study population and NHANES 2007-2010 population.

[†]For the NHANES 2007-2010 population, percentages only are presented because of complex survey design/weighting.

[‡]The SCORAD index was completed for all patients with atopic dermatitis.

[§]Among those reporting systemic corticosteroid use based on the last year's reported intake.

section in this article's Online Repository at www.jacionline.org. Mean differences were determined by means of multivariate linear regression, adjusting for age, sex, and race/ethnicity. Analyses were completed with STATA SE/12.1 software (College Station, Tex).

Overall, study participants were predominantly male (78.1%), with a larger percentage of children of "other" race (37.5%) than

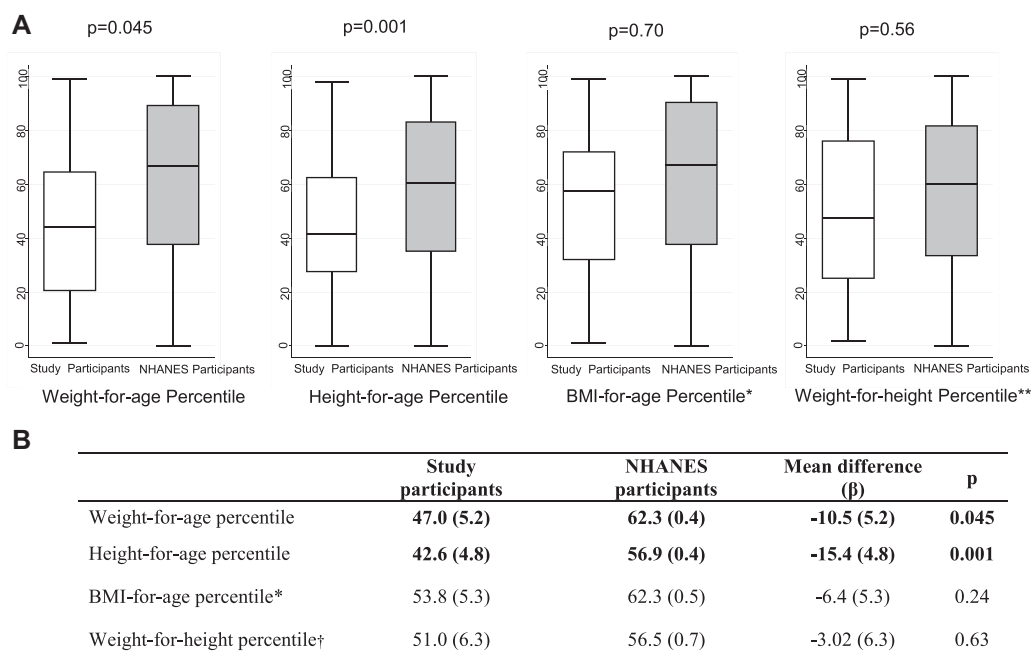


FIG 1. Anthropometric features of the study population with food allergy compared with the general population of children (NHANES 2007-2010). **A**, Box plots of mean weight-for-age, height-for-age, BMI-for-age, and weight-for-height percentiles in the study population and NHANES 2007-2010 children. **B**, Mean percentile differences between children with food allergy and NHANES 2007-2010 children, as determined by using multivariate linear regression and adjusting for age, sex, and race/ethnicity. Values are reported as means (SEs). Recumbent length was substituted for height in children less than 24 months of age. *Excluding children less than 2 years old. †For children less than 121 cm in height.

the general population (7.9%, Table I). Most participants restricted milk (87.5%), egg (81.3%), soy (81.3%), wheat (59.4%), and/or peanut (87.5%); more than half (56.3%) avoided all 5 major allergens; and all avoided at least some additional foods. Amino acid-based formula intake comprised 17% to 100% of daily energy intake, with 42.3% taking more than half of their calories from formula (Table I); 2 children consumed only formula. Of the children, 40.6% reported intake of vitamins/supplements in addition to formula, and 46.9% had exposure to systemic corticosteroids in the past year (median steroid days, 10). Most children had mixed (28.1%) or non-IgE-mediated food allergy (46.9%, which is further defined in the Methods section in this article's Online Repository), 43.7% had EGID, 53.1% had atopic dermatitis, and 9.4% had a gastrostomy tube.

Participants had decreased weight-for-age ($P = .045$) and height-for-age ($P = .001$) percentiles and trends toward lower BMI and weight-for-height percentiles (Fig 1). Although many children did not reach recommended intakes of daily total fiber (60.9%), most attained adequate caloric intake (81.5%), reaching 80% or greater of the estimated energy requirement (see Table E1 in this article's Online Repository at www.jacionline.org). Most also obtained adequate micronutrient intake; a notable exception was vitamin D, with 55.6% having an estimated intake of less than 67% of the recommended dietary allowance, which is consistent with nationwide trends (see Table E2 in this article's Online Repository at www.jacionline.org). No other dietary deficiencies in macronutrients or micronutrients were detected. Participants were frequently observed to have estimated intake of greater than the tolerable upper level for niacin (25.9%), zinc (59.3%),

magnesium (25.9%), and copper (29.6%), the significance of which is unclear.

Laboratory assessment demonstrated that 48.4% had serum 25-OH vitamin D levels in the "insufficient" or "deficient" range, but other nutritional measures (albumin, hemoglobin, iron, calcium, and phosphate) were not notably decreased (see Table E3 in this article's Online Repository at www.jacionline.org). Serum folate levels were frequently (58.1%) greater than the detection level of our laboratory assay (24 ng/mL), and 35.5% had increased vitamin B12 levels. We found that although many (50.0%) children had plasma choline z scores of less than -1.0 (see Fig E1 in this article's Online Repository at www.jacionline.org), there was no significant correlation between choline z scores and either aspartate transaminase, alanine transaminase, or creatine phosphokinase levels, and thus clear evidence of end-organ damage was absent. A significant positive trend between choline z scores and percentages of energy intake from amino acid-based formula was noted.

Despite appropriate daily energy intake, participants were smaller than children in the general population. This is consistent with previous studies, which have suggested that milk allergy, multiple food allergies, and early onset of food allergy are potential risk factors for poor growth⁴⁻⁶; most participants in our study have some or all of these characteristics. Although deficiencies in select nutrients, such as vitamin D, were noted, most children attained adequate intake of other nutrients. Study participants were at risk for low daily fiber intake, but other macronutrient intakes were appropriate. With regard to choline, although plasma levels were overall low and intake was limited by dietary restrictions of choline-rich foods, there was no

evidence of end-organ damage. The positive relationship between formula intake and choline levels suggests that increased formula consumption can provide choline in place of natural food sources.

As in previous studies, growth differences in this population were not clearly explained by inadequate caloric intake. The mechanisms that might explain poor growth despite adequate energy intake are unclear but are likely multifactorial, potentially including systemic corticosteroid exposure (because of comorbid conditions), intermittent or chronic gastrointestinal inflammation (eg, in patients with EGID), and increased metabolic demands caused by conditions such as atopic dermatitis.⁶ Furthermore, although amino acid-based formulas might provide appropriate protein equivalents, it is unknown whether these have different effects on growth compared with natural or animal-based protein sources.

The limitations of this study include reliance on a 3-day food record for nutritional assessment, although error is likely minimized in this population because of the limited variety of participants' diets. A nonallergic control population was not used; however, we compared anthropometric measurements with the large, nationally representative NHANES 2007-2010 population, which is reflective of recent trends in growth and obesity. Participants were selected from a referral population/tertiary care center, and selection bias of consenting participants might have led to overrepresentation of children with nutritional concerns.

With the increasing prevalence of food allergy in recent decades, it is very important that we recognize the effect of food allergy on growth and nutrition. Although children with extensive food allergy requiring formula supplementation appear to have generally adequate dietary intake, we found evidence of select macronutrient and micronutrient deficiencies and select micronutrient excess, and despite normal energy intakes, both weight and height were lower than in the NHANES 2007-2010-derived control population. Given these concerns, further research is clearly needed regarding the nutritional consequences of food allergy, especially research including this group with extensive dietary restriction.

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METHODS

Children were categorized by allergy type, which was defined as “IgE mediated,” “non-IgE mediated,” or “mixed.”^{E1} We defined allergy type as follows: children whose history involved classic IgE symptoms (including rash, angioedema, respiratory changes, vomiting, and anaphylaxis) with supportive specific IgE testing (ImmunoCAP) to suspected food or foods were considered to have “IgE-mediated” allergy; children with a history of symptoms of food protein–induced enterocolitis, EGID without positive specific IgE levels to foods, or other suspected food allergy without positive specific IgE levels to foods were considered to have “non-IgE-mediated” allergy; and children with EGID and positive specific IgE levels to food or foods or with a history consistent with both types of allergy defined above were considered to have “mixed” allergy.

Age-adjusted percentiles for anthropometric measures were calculated by using the CDC’s Epi Info software package (Epi Info version 3.5.4, July 23, 2008), as follows: if less than 24 months of age, weight-for-age, length-for-age, and weight-for-length percentiles were calculated by using World Health Organization growth curves^{E2}; if 24 months or older, weight-for-age, height-for-age, and BMI-for-age percentiles were determined by using CDC (2000) curves.^{E3} Weight-for-height or weight-for-length percentiles were determined for all children with a height or length of less than 121 cm. Data from children in NHANES 2007–2010 within the age range of study participants was used as for comparison of growth measurements with the study group. NHANES is a continuously obtained, nationally representative cross-sectional survey of the civilian noninstitutionalized population and uses a complex multistage probability design, with oversampling of certain subpopulations (ie, non-Hispanic blacks, Hispanics, and those with low income). Logistic regression using

survey weights provided by NHANES were used for these analyses, with the clinical population each assigned a weight of 1. Analyses were adjusted for age, sex, and race/ethnicity. Approval of study procedures for NHANES was obtained through the National Center for Health Statistics Ethics Review Board. A full description of NHANES procedures is available elsewhere.^{E4,E5}

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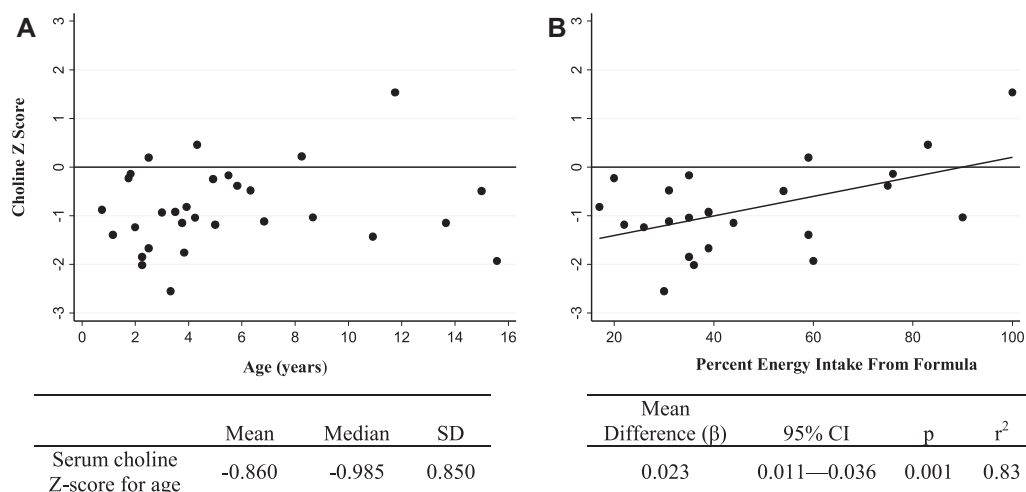


FIG E1. A, Serum choline levels of study participants shown as z scores for age ($n = 30$), with mean and median values listed below. **B,** Choline z scores versus the percentage of daily energy intake consumed from amino acid-based formula, as determined by using multivariate linear regression and adjusting for age; sex; avoidance of milk, egg, peanut, wheat, and soy; and serum aspartate transaminase, alanine transaminase, and creatine phosphokinase levels.

TABLE E1. Estimated energy requirement and intake of subjects

Participant	Sex	Age (y)	EER (kcal/d)	Reported intake (kcal/d)	Percentage intake vs EER
1	M	4.9	—	—	—
2	M	3.5	1650	1597	96.8
3	M	4.3	1506	1181	78.4
4	M	11.8	2509	2351	93.7
5	F	1.2	757	678	89.6
6	M	2.5	881	1074	121.9
7	M	3.8	1582	1167	73.8
8	M	15.0	2625	2437	92.8
9	F	6.8	1643	1537	93.5
10	M	13.7	—	—	—
11	M	5.5	1737	1582	91.1
12	M	10.9	—	—	—
13	M	3.8	—	—	—
14	M	0.8	803	823	102.5
15	M	15.6	2366	2288	96.7
16	F	3.0	1371	826	60.2
17	M	6.3	1779	1796	101.0
18	F	3.3	1380	950	68.9
19	M	5.8	1500	1230	82.0
20	M	5.0	1697	2048	120.7
21	M	2.5	979	1339	136.7
22	M	2.0	881	1880	213.4
23	M	1.8	816	1271	155.8
24	F	8.7	1588	1618	101.9
25	M	1.8	958	790	82.5
26	M	4.3	1626	1566	96.3
27	F	8.3	—	—	—
28	M	2.3	1059	1816	171.5
29	M	3.9	1264	1537	121.6
30	M	2.3	1415	1272	89.9
31	F	2.4	1112	809	72.8
32	M	15.8	2672	2755	103.1

Reported intake was based on the 3-day diet record. Five children who did not return 3-day food records are indicated by “—”. Those with energy intake of less than 80% EER are shown in boldface.

EER, Estimated energy requirement (calculated from age, sex, and activity level).

TABLE E2. Macronutrient and micronutrient intake of subjects

	Below recommendation, no. (%)	Adequate, no. (%)	Above recommendation, no. (%)*
Macronutrients			
Carbohydrate	2 (7.4)	25 (92.6)	0 (0)
Total protein/amino acid	0 (0)	27 (100)	0 (0)
Total fat	5 (18.5)	15 (55.6)	7 (25.9)
Fiber†	14 (60.9)	9 (39.1)	—
Micronutrients			
Calcium	4 (14.8)	22 (81.5)	1 (3.7)
Copper	0 (0)	19 (70.4)	8 (29.6)
Folate‡	2 (7.4)	22 (81.5)	3 (11.1)§
Iron	0 (0)	27 (100)	0 (0)
Magnesium	0 (0)	20 (74.1)	7 (25.9)
Niacin	0 (0)	20 (74.1)	7 (25.9)§
Zinc	0 (0)	11 (40.7)	16 (59.3)
Vitamin B12‡	1 (3.7)	26 (96.3)	—
Vitamin D	15 (55.6)	12 (44.4)	0 (0)
Vitamin E‡	1 (3.7)	26 (96.3)	0 (0)§
Vitamin K‡	5 (18.5)	22 (81.5)	—

Percentages for “Adequate” macronutrient intake were calculated from the number of participants with completed food records ($n = 27$) within the age-specific acceptable macronutrient distribution range for nutrients (as published by the Food and Nutrition Board of the Institute of Medicine). Subjects were listed as “Below recommendation” or “Above recommendation” if outside the normal range. The exception was fiber, for which children more than 2 years old were listed as either “Adequate” or “Below recommendations” based on American Academy of Pediatrics guidelines (1995; calculated as follows: Grams = Age in years + 5) in place of the acceptable macronutrient distribution range. Percentages for “Adequate” micronutrient intake were calculated from the number of participants consuming 67% or more of the recommended dietary allowance (or adequate intake if the recommended dietary allowance was not established) but less than the tolerable upper limit for the nutrient (as published by the Food and Nutrition Board of the Institute of Medicine). Subjects were listed as “Below recommendation” if consuming less than 67% of the recommended dietary allowance for the nutrient and listed as “Above recommendation” if consuming the tolerable upper limit or more for the nutrient.

*For children younger than 12 months, acceptable macronutrient distribution ranges (carbohydrate, protein/amino acid, and fat) are not established. Therefore adequate intake was used instead, and the patient was either categorized as “Below recommendation” or “Adequate” for 1 subject in this age range.

†Children younger than 2 years ($n = 4$) were excluded from fiber calculation because of the lack of consensus in the recommendations for appropriate intake in this age range.

‡If the micronutrient does not have an associated tolerable upper limit determined (vitamin B12 and vitamin K, also folate and vitamin E for children <12 months of age), subjects were either categorized as “Below recommendations” or “Adequate.”

§The tolerable upper limit for folate (folic acid), niacin, and vitamin E for intake of synthetic forms only.

TABLE E3. Laboratory assessment (n = 31)

Test	Median (25th-75th percentile)	Less than normal range, no. (%)	
Albumin (g/dL)	4.7 (4.5-4.8)	0 (0)	
Calcium (mg/dL)	9.9 (9.5-10.2)	0 (0)	
Hemoglobin (g/dL)	13.1 (12.4-13.6)	3 (9.7)	
Iron (serum; µg/dL)	91 (71-103)	3 (9.7)	
Phosphate (mg/dL)	4.6 (4.5-5.1)	0 (0)	
	Median (25th-75th percentile)	Greater than normal range, no. (%)	
AST (U/L)	32 (28-38)	11 (35.5)	
ALT (U/L)	15 (13-24)	2 (6.5)	
CPK (U/L)	128 (95-145)	3 (9.7)	
	Deficient, <20 ng/mL, no. (%)	Insufficient, 20-31 ng/mL, no. (%)	Sufficient, ≥32 ng/mL, no. (%)
25-OH vitamin D (ng/mL)	4 (12.9%)	11 (35.5)	16 (51.6)
	<5.3, no. (%)	5.3-24.0 (normal range), no. (%)	≥24.0, no. (%)
Serum folate (ng/mL)	1 (3.2%)	12 (38.7)	18 (58.1)
	<200, no. (%)	200-900 (normal range), no. (%)	>900, no. (%)
Vitamin B12 (pg/mL)	1 (3.23%)	19 (61.29)	11 (35.48)

ALT, Alanine transaminase; AST, aspartate transaminase; CPK, creatine phosphokinase.