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Systematic Review of Nutrient Intake and Growth in Children with Multiple IgE-Mediated Food Allergies

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Abstract

Background: Food allergies affect up to 8% of American children. The current recommended treatment for food allergies is strict elimination of the allergens from the diet. Dietary elimination of nutrient-dense foods may result in inadequate nutrient intake and impaired growth. The purpose of this review was to critically analyze available research on the effect of an elimination diet on nutrient intake and growth in children with multiple food allergies. **Methods:** A systematic review of the literature was conducted and a workgroup was established to critically analyze each relevant article. The findings were summarized and a conclusion was generated. **Results:** Six studies were analyzed. One study found that children with food allergies are more likely to be malnourished than children without food allergies. Three studies found that children with multiple food allergies were shorter than children with 1 food allergy. Four studies assessed nutrient intake of children with multiple food allergies, but the inclusion and comparison criteria were different in each of the studies and the findings were conflicting. One study found that children with food allergies who did not receive nutrition counseling were more likely to have inadequate intake of calcium and vitamin D. **Conclusion:** Children with multiple food allergies have a higher risk of impaired growth and may have a higher risk of inadequate nutrient intake than children without food allergies. Until more research is available, we recommend monitoring of nutrition and growth of children with multiple food allergies to prevent possible nutrient deficiencies and to optimize growth. (*Nutr Clin Pract.* XXXX;xx:xx-xx)

Keywords

food hypersensitivity; vitamin; micronutrient; soy foods; nutrition therapy

Introduction

Food allergies affect up to 8% of American children younger than 18 years, and the prevalence of food allergy appears to be increasing.¹ Eight foods account for more than 90% of food allergies: milk, soy, wheat, eggs, peanuts, tree nuts, fish, and shellfish,² but more than 170 foods have been identified to cause allergic reactions.³ Currently, the recommended treatment for food allergies is strict elimination of the offending allergens from the diet. Elimination of nutrient-dense foods from the diet, however, may result in poor nutrient intake and impaired growth in children.

The effect of eliminating milk from the diet on growth and development has been clearly documented in the literature and is well understood by many clinicians. Children following a milk-free diet are more likely to consume less energy, fat, protein, calcium, riboflavin, and niacin than are milk consumers.⁴ Children with milk allergy are at increased risk of having impaired growth compared to healthy children.⁵ Furthermore, research has demonstrated that nutrition counseling and consumption of an age-appropriate milk substitute led to improved nutrient intake in children following a milk-free diet.⁶

Few studies have looked at the effect of a multiple-food-elimination diet on nutrient intake and growth. The purpose of this article is to critically analyze the current research on the effect of a multiple-food-elimination diet on nutrient intake and growth in children with multiple food allergies.

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Methods

We searched for primary research studies to answer the following question: Are children with 2 or more food allergies at risk of inadequate nutrient intake and impaired growth? We used strict inclusion and exclusion criteria to search the PubMed and CINAHL databases using the following MeSH terms: food hypersensitivity and growth, food hypersensitivity and nutrition, food hypersensitivity and micronutrient, food hypersensitivity and vitamin, and food hypersensitivity and trace element. The MeSH search term *food hypersensitivity* includes the top 8 food allergens except soy. Therefore, the search was repeated with *soy hypersensitivity*. Studies with only an abstract published were excluded. We followed the Academy of Nutrition and Dietetics' (AND) Evidence Analysis Process to search for and critically review relevant articles.⁷ Two different researchers (PSG and CS) critically appraised each article using the AND's Quality Criteria Checklist: Primary Research. The results were compared and discussed by the workgroup. A quality rating was given to each article. Statistically significant findings related to nutrition and growth of children with multiple food allergies were extracted from all articles that met our inclusion criteria, even when other outcomes were the primary focus of the study.

Inclusion Criteria for Systematic Review of the Literature

- IgE-mediated food allergy proven by skin prick testing or serum-specific IgE and/or food challenge
- Subjects with 2 or more food allergies
- Age 0–18 years
- Primary study
- Written in English
- Published 1990 or later
- Human research

Exclusion Criteria for Systematic Review of the Literature

- Abstract only
- Medical conditions other than asthma, atopic dermatitis, and other atopic manifestations

Results

Nearly 900 studies were identified in the literature search. Screening for duplications and eligibility greatly reduced the number of articles to be critically analyzed to 6. The number of studies screened, assessed, and reported in this review are listed in Figure 1. A total of 6 studies with 415 subjects and 335 controls were included in this review. There were 3 cross-sectional studies, 2 non-controlled studies, and a case series; each was of neutral quality. Relevant findings of the studies are summarized in Table 1.

Relationship of Multiple Food Allergies to Growth

All of the studies reviewed reported on the growth status of children with multiple food allergies. The World Health Organization (WHO) defines malnutrition as a weight-for-age, weight-for-length, or length-for-age z-score < -2 .⁸ One cross-sectional study found that children with food allergies were more likely to be malnourished than controls as indicated by a weight-for-age or height-for-age z-score < -2 ($P < .05$).⁹ The same study also found that children with 3 or more food allergies were more likely than children with 1 or 2 food allergies to be malnourished as indicated by a weight-for-age or height-for-age z-score < -2 ($P < .05$).⁹ All other studies found that growth of children with multiple food allergies was within normal limits as defined by a z-score of 2 to -2 or 3rd to 97th percentile on the growth chart.^{10–13} However, 4 of these studies found differences between the growth of children with multiple food allergies and the control group.^{9,10,11,14} Three studies found that children with multiple food allergies were shorter than children with 1 food allergy ($P < .05$),^{10,11,14} while a single study found that weight-for-age z-scores decreased as the number of sensitized food allergens increased ($P < .01$).¹¹

Relationship of Multiple Food Allergies to Nutrient Intake

Four of the studies reviewed assessed nutrient intake. Two studies found that children with food allergies consumed more vitamin E than did controls ($P < .05$).^{9,10} Flammarión et al reported that children with food allergies consumed more vitamin A than did controls ($P < .05$).⁹ One study found that children with food allergies who did not receive nutrition counseling were more likely to have inadequate intake of calcium and vitamin D ($P < .05$).¹⁰ This study also reported that children with milk allergy were more likely to consume inadequate calcium than children with other allergies ($P < .05$).¹⁰ One study reported adequate protein intake in children with multiple food allergies consuming amino-acid-based formula,¹³ while another reported possible essential fatty acid (EFA) deficiency in children with multiple food allergies [$P < .01$ for the $(\omega 3 + \omega 6) / (\omega 7 + \omega 9)$ ratio].¹²

Discussion

Eliminating multiple foods from the diet of growing children may result in poor nutrient intake and poor growth. Our review of the literature unveiled 6 studies of neutral quality related to this topic. Limitations of this review include inconsistency of methods and exclusion criteria among the studies. Some studies excluded specific comorbidities while others did not. In addition, 1 study included all patients with food sensitizations but did not specifically state if the sensitized allergens were relevant food allergies or if the sensitized foods were actually

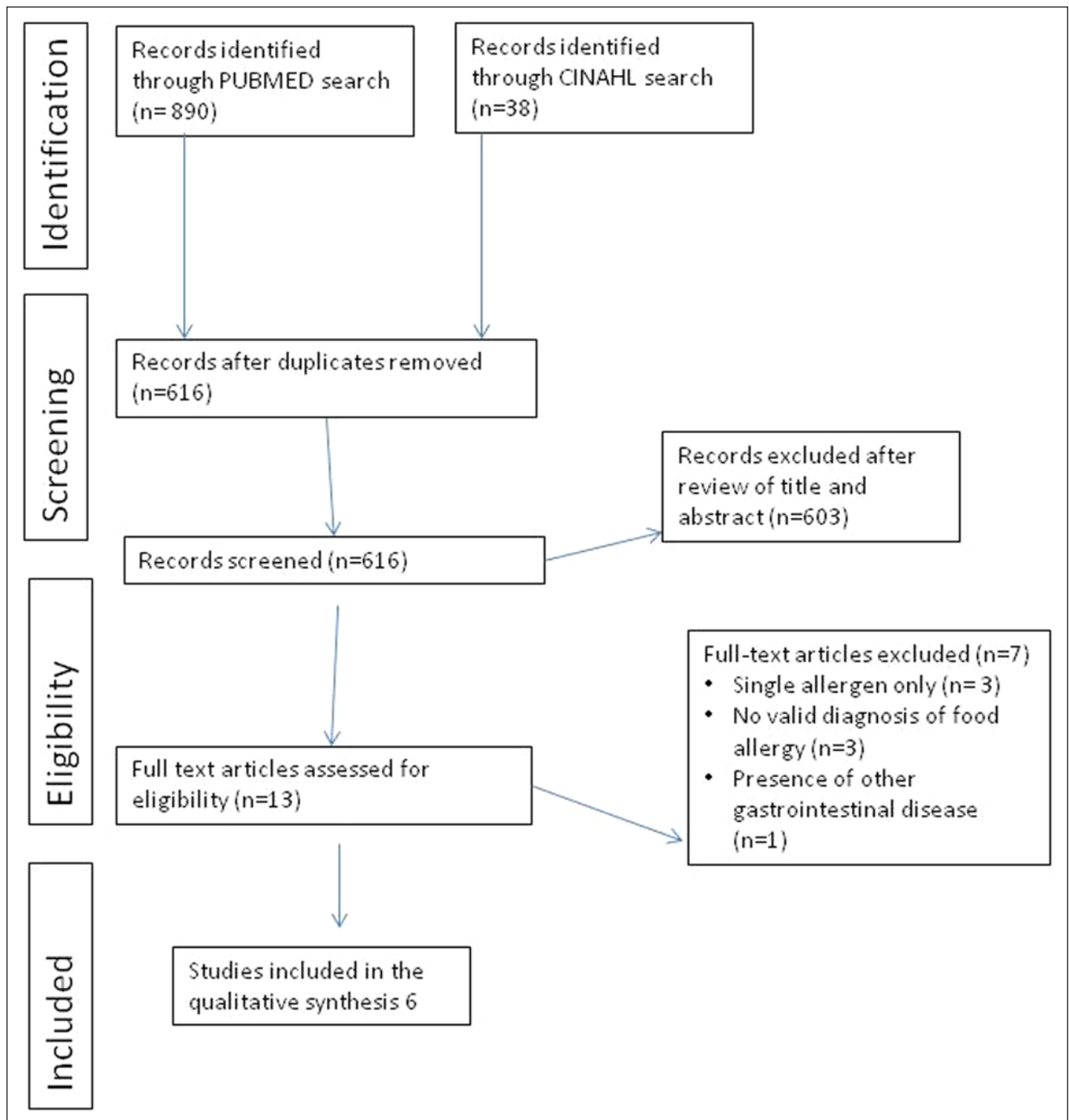


Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram. Based on the PRISMA flow diagram.²⁶

eliminated from the diet. Another limitation is that the studies used different nutrition assessment methods and used different nutrient intake standards. This led to inconsistent results that did not prompt a clear conclusion.

Growth

Five of the 6 studies reported that the growth of children with multiple food allergies was within normal limits.¹⁰⁻¹⁴ Only 1

Table 1. Overview of Studies (n = 6).

Study, Design, Class/ Rating	Subjects	Comparison Group	Relationship of MFA to Growth (Standard Used)	Relationship of MFA to Nutrient Intake (Nutrition Assessment Method/Standard Used)	Limitations & Comments
Christie et al (2002), ¹⁰ cross-sectional, class D, rating Ø ^a	consecutive patients with ≥ 1 FA (n = 98) age 3.7 ± 2.3 years	age-matched controls without FA (n = 99)	(CDC growth charts) ≥ 2 FA more likely to be < 25th percentile height-for-age than 1 FA ^b (35% and 16%, respectively) 1 FA more likely to be > 75th percentile height-for-age than ≥ 2 FA ^c (34% and 13%, respectively)	(3-day food record/10th edition DRIs) ≥ 1 FA more likely to consume > 100% DRI for vitamin E than controls ^b (78% and 92%, respectively) milk allergy more likely to consume < 100% DRI for calcium than other allergies ^b (58% and 31%, respectively) other allergies more likely to consume < 100% DRI vitamin E than milk allergy ^b (90% and 62%, respectively) FA without nutrition counseling more likely to consume < 67% DRI for calcium and vitamin D than those with counseling ^a (calcium: 39% and 15%, respectively; vitamin D: 55% and 29%, respectively) (3-day food record/RDI for healthy children in France)	used 25th percentile height-for- age as indicator of potential undernutrition did not report weight data unknown time avoiding allergens
Flammarion et al (2011), ⁹ cross- sectional, class D, rating Ø	children with ≥ 1 FA (n = 96) age 4.6 ± 2.58 years	age- and sex- matched controls (n = 95)	(Sempé reference values) ≥ 3 FA more likely to have weight- for-age and height-for-age z-score < -2 than children with 1-2 FA ^b (weight: 14.5% and 1.8%, respectively; height: 12.1% and 3.6%, respectively) FA more likely than controls to have weight-for-age and height- for-age z-scores < -2 ^b (weight: 9.3% and 0%, respectively; height: 7.2% and 2.7%, respectively) (Korean growth charts)	FA consumed more vitamins A and E than controls ^b (vitamin A: 95% RDA and 65% RDA, respectively; vitamin E: 92% RDA and 53% RDA, respectively)	88% of children with food allergies received nutrition counseling by a dietitian avoiding allergens for ≥ 4 months prior to study
Cho et al (2011), ¹¹ case series, class D, rating Ø	children with atopic dermatitis (n = 165) classified according to # sensitized FA	Korean Pediatric Society growth charts 2007	weight-for-age z-score decreased as # sensitized FA increased ^c (-0.21 ± 1.08, 0.02 ± 0.87, -0.14 ± 0.96, and -0.57 ± 1.90 for 0, 1, 2, and ≥ 3 sensitized FA, respectively)		unknown time avoiding allergens did not state if they were actually avoiding the sensitized FA

(continued)

Table 1. (continued)

Study, Design, Class/ Rating	Subjects	Comparison Group	Relationship of MFA to Growth (Standard Used)	Relationship of MFA to Nutrient Intake (Nutrition Assessment Method/Standard Used)	Limitations & Comments
Aldamiz-Echevarría et al (2008), ¹² cross- sectional, class D, rating Ø	age 16.00 ± 10.93 months children with ≥ 2 FA (n = 25)	healthy children (n = 61)	≥ 3 FA significantly shorter than 1 FA ^b (−0.50 ± 1.01 and 1.10 ± 0.90, respectively) WNL	(no nutrition assessment measure used/no nutrient intake standard used)	unknown time avoiding allergens
	age 3.8 ± 1.6 years	age 5.1 ± 2.6 years		EFA index [(ω3 + ω6) / (ω7 + ω9)] was lower in FA than controls ^c (1.5 and 1.9, respectively) DHA:DPA ratio was lower in FA than controls ^c (4.0 and 11.7, respectively) lower percentage of α-linoleic acid in FA than controls ^b (27.4 and 30.7, respectively) (diet record/RDA)	diets of the control patients were not described
Sicherer et al (2001), ¹³ children non-controlled trial, class D, rating Ø	children with milk allergy (n = 18) ≥ 16 had multiple food allergies age 6–210 months at enrollment	NCHS z-scores, RDA	(NCHS)	consumed 152 ± 12% RDA for protein from formula at 4 months	unknown time avoiding allergens
			weight-for-age, height-for-age, and weight-for-height z-scores WNL at entry, 1 month, 4 months (−0.8 ± 0.2, −0.3 ± 0.2, and −0.6 ± 0.3, respectively, at 4 months) no statistically significant differences in z-scores between 0, 1, and 4 months		unclear how many had 18 MFA vs only milk allergy
Zeiger et al (1999), ¹⁴ non-controlled trial, class D, rating Ø	children with allergy to milk and soy (n = 13) 11 had additional allergies age 23.4 ± 2.5 months at enrollment	children with milk allergy but no soy allergy (n = 80)	(NCHS)		funded by formula manufacturer primary purpose to test efficacy of formula many with allergic eosinophilic gastroenteritis unknown time avoiding allergens
			children with milk and soy allergy had lower height-for-age z-scores than children with milk allergy ^b (−0.73 ± 0.26 vs −0.09 ± 0.12)		purpose of study was to assess prevalence of soy allergy in children with milk allergy
		age 18.4 ± 0.9 months			weight & height for milk and soy allergic children measured only 1 time

CDC, Centers for Disease Control and Prevention; DHA, docosahexanoic acid; DPA, docosapentaenoic acid; DRI, dietary reference intake; EFA, essential fatty acid; FA, food allergy; MFA, multiple food allergies; NCHS, National Center for Health Statistics; RDA, recommended daily allowance; RDI, reference daily intake; WNL, within normal limits.

^aClass and rating were determined using the Academy of Nutrition and Dietetics' *Evidence Analysis Manual*. Ø = neutral.
^bP < .05.
^cP < .01.

study reported that children with 3 or more food allergies were more likely to be malnourished than children with 1 or 2 food allergies.⁹ This study was different from the others in 2 ways: 88% of the subjects received nutrition counseling from a trained dietitian, and all subjects were avoiding the allergens for at least 4 months prior to the study visit. It is unclear when the dietitian visit occurred. If the dietitian visit occurred at or close to the time that anthropometric measurements were taken for the study, the impact of nutrition counseling would not be seen in the anthropometric measurements. It is most likely that Flammarion et al⁹ found a higher incidence of malnutrition than the other studies because they were the only investigators who excluded patients who eliminated offending foods for fewer than 4 months.

Four of the 6 studies found differences in the growth of children with food allergies and controls. Three studies found that children with food allergies were shorter than children without food allergies. This may indicate potential undernutrition. Since growth in early childhood affects overall adult stature,¹⁵ this is an important finding that may be clinically significant.

Previous studies have found that children with atopic dermatitis, which is frequently associated with food allergies, may have poor growth.^{16,17} These studies have found that children with atopic dermatitis are shorter than controls. Studies have also found that asthmatic children treated with inhaled corticosteroids initially experience a decline in growth velocity that may contribute to shorter stature.^{18,19} This suggests that there may be other mechanisms involved in the poor growth of children with multiple food allergies besides food exclusion alone.

Nutrient Intake

Four of the studies reported on nutrient intake. All of the studies used different nutrient intake standards, which makes it difficult to compare the studies to each other. Two studies found that children with food allergies consumed more vitamin E than did controls.^{9,10} More than 50% of the patients in both studies received nutrition counseling. Nutrition counseling for children with multiple food allergies often includes recommending oil supplementation to increase calorie and fat intake. The additional oil in their diets may have resulted in the increased vitamin E intake reported. It is interesting that the increased intake of vitamin E was the only consistent result reported by the studies that measured nutrient intake.

One study found that children with milk allergies are more likely to consume < 100% of the dietary reference intake (DRI) for calcium than are children with other allergies.¹⁰ The effects of milk allergy on nutrient intake and growth are well documented in the literature.⁴⁻⁶ However, these studies were done prior to the widespread availability of amino-acid formulas. Studies have documented improved growth since the introduction of amino-acid-based formulas.²⁰ This improvement in growth with amino-acid-based formulas is likely multifactorial. In addition to symptom improvement that may improve nutrient intake, these formulas probably result in reduction of inflammation,

which may in turn improve nutrient absorption and normalization of cytokines positively impacting growth.

One study found that children who did not receive nutrition counseling were more likely to consume < 67% DRI for calcium and vitamin D than were children with nutrition counseling.¹⁰ This is an important finding, as it suggests that nutrition counseling may improve calcium and vitamin D intake of children with food allergies.

Children with food allergies who received nutrition counseling consumed more calcium than did those who did not receive nutrition counseling in the study by Christie et al.¹⁰ It is unfortunate that nutrition counseling was poorly defined in this study. Another study, in which 88% of the subjects received nutrition counseling from a trained dietitian, found that nutrient intake was similar in children with food allergies and controls.⁹ The nutrition counseling may have influenced their food choices and thus their nutrient intake.

A study from Spain reported that children with multiple food allergies are more likely to have EFA deficiency than are controls.¹² In this study, the EFA index $[(\omega 3 + \omega 6) / (\omega 7 + \omega 9)]$, which can be an indicator of EFA status,²¹ was lower in the children with food allergies. Docosapentaenoic acid (22:5 ω 6) is produced when docosahexanoic acid (DHA) (22:6 ω 3) availability is marginal, and the ratio between DHA and docosapentaenoic acid can be used as an indicator of DHA status.²² In the study by Aldámiz-Echevarría et al, children with food allergies appear to have low DHA status. However, since the best biomarkers of dietary fatty acids are those fatty acids that cannot be synthesized endogenously, linoleic and α -linoleic acids may be better indicators, as they tend to be less affected by dietary intake.²³ The children with food allergies had lower serum linoleic acid concentrations, but their α -linoleic acid concentrations were not different. The children in both groups did not differ with regard to mead acid and arachidonic acid concentrations, which are the numerator and denominator of the triene:tetraene ratio, making it unlikely that any of the children in either group were EFA deficient.

Future Research

Our review of the literature highlights the need for additional research surrounding the growth and nutrition status of children with multiple food allergies. The heterogeneity of this population makes research difficult. Future studies could include multicenter research so that sample sizes are adequate to divide patients by specific allergies. We also speculate that categorizing children by type of allergy may be superior to dividing by number of food allergies since certain food allergies or combinations of food allergies may be nutritionally more important than others. For instance, in the Western world, a combination of a cow's milk and soy allergy in a toddler may be more nutritionally relevant than an allergy to peanuts and shellfish. However, nutritionally important allergies may differ depending on the population that is studied and the usual diet of that population. Many of the articles reviewed assessed

nutrient intake and growth only at a single point in time. Future research should follow children with multiple food allergies over a period of time to describe changes in nutrient intake and growth in response to medical nutrition therapy. In addition, future research should compare subjects with and without nutrition intervention to assess the impact of nutrition intervention on nutrient intake and growth.

The results of this systematic review suggest that children with multiple food allergies following a multiple-food elimination diet may grow less well than children without food allergies. Over the last few decades, eosinophilic gastrointestinal disease, specifically eosinophilic esophagitis (EoE), has been increasingly identified in the population of children with food allergies.²⁴ EoE is associated with failure to thrive and feeding disorders.²⁵ Future studies should determine the role of such disorders in children with multiple food allergies who have poor growth.

Application to Practice

The available research specific to our research question is limited and the quality of the available studies is neutral. One study found that children with 3 or more food allergies are more likely to be malnourished than are children with 1 or 2 food allergies,¹ while other studies found that children with multiple food allergies grew less well than controls, but still within the normal range. Our review of the literature shows that children with multiple food allergies have a higher risk of impaired growth. Regarding nutrient intake, 2 of the studies reviewed did not find that children with multiple food allergies have inadequate nutrient intake. However, 1 study found that children with milk allergy consumed less calcium and vitamin D than did children with other allergies and that children with food allergies who received nutrition counseling were less likely to have inadequate calcium and vitamin D intake.¹⁰ Thus, we cannot rule out that children with food allergies may be at risk of inadequate nutrient intake. Reducing the risk of poor nutrition and poor growth is especially important in childhood, as poor nutrition in early childhood can affect growth and development throughout the lifespan.¹⁵ Until more research is available, we recommend ongoing nutrition and growth assessment of children with multiple food allergies to prevent possible nutrient deficiencies and optimize growth and development. This is consistent with the National Institutes of Allergy and Infectious Diseases guidelines, which recommend regular growth assessment and nutrition counseling for children with food allergies.¹

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