

Letter to the Editor

Impact of food allergy on the growth of children with moderate-severe atopic dermatitis*To the Editor:*

Atopic dermatitis (AD) is a chronic inflammatory skin disease that affects 10% to 20% of children in the United States, with 1 of 3 of those affected having moderate to severe disease.¹ Significant sleep disturbance due to itching and increased metabolic demands due to rapid skin turnover and chronic inflammation are hypothesized to impact the growth of children with AD.^{2,3} Between 15% and 40% of children with AD have food allergy (FA) as well, which alone can have adverse growth consequences.^{4,5} However, few studies to date have examined the role that coexistent food allergy has on the growth of children with AD. Here, we sought to examine the height, weight, and body mass index (BMI) Z scores of children 2 to 20 years of age with moderate-severe AD enrolled in a natural history of AD protocol. We categorized the children into 3 groups based on their FA status: (1) those with IgE-mediated FA to the most common food allergens—cow's milk, egg, wheat, soybean, and/or peanut (IgE FA; $n = 42$; mean age: 9.7 ± 4.6 years); (2) those avoiding any of these 5 foods due to worsening of their AD on ingestion of the food (skin only; $n = 10$; mean age: 8.4 ± 3.6 years); (3) those clinically nonallergic to food following an unrestricted diet (no FA; $n = 25$; mean age: 10.3 ± 3.6 years) (Table I). Additional details regarding clinical phenotyping are provided in the Online Repository (available at www.jacionline.org). Statistical analyses were performed with STATA 14.2 software (StataCorp, College Station, Tex). Unadjusted comparisons were made using ANOVA and Fisher exact test for continuous and dichotomous variables, respectively. Adjusted comparisons were performed using linear regression. Continuous variables are listed as the mean $\pm$ SD.

The number of subjects avoiding each of the 5 foods in the IgE FA and skin only groups is depicted in Table E1 (in this article's Online Repository available at www.jacionline.org). Peanut was the most commonly avoided food in both groups, followed by egg and milk: 30 of 42 (71%) and 6 of 10 (60%) of the IgE FA

and skin only subjects were avoiding 2 or more foods, respectively (Table E1). The majority of children with FA developed the disease early in life; the median percentage of life that each food was avoided is listed in Table E2 (in this article's Online Repository available at www.jacionline.org). Prior to enrollment, 2 subjects had outgrown a milk allergy, 3 an egg allergy, and 1 a wheat allergy. Although these FAs are often outgrown, some studies suggest that children with moderate-severe eczema have a reduced likelihood of outgrowing milk and egg allergy.^{6,7} No significant differences in age, duration of AD, total IgE levels, peripheral eosinophil counts, use of steroids or immunomodulators, or severity of AD as assessed by Scoring Atopic Dermatitis (SCORAD) were found across the 3 groups (Table I, Fig 1, A). The IgE FA group had a slight male predominance compared with the no FA group (Table I). Mean SCORADs in the IgE FA, skin only, and no FA groups were 46 ± 16 , 51 ± 16 , and 41 ± 15 , respectively. Asthma was most common in the IgE FA cohort, and 4 of these subjects had been diagnosed with eosinophilic esophagitis (EoE) (Table I). Allergic rhinitis was common in all 3 groups (Table I).

In models adjusting for age, sex, asthma, and EoE, the BMI Z score (0.08 ± 0.98) and weight Z score (-0.42 ± 1.12) of the IgE FA group were both significantly lower than in the skin only (BMI Z: 0.77 ± 1.07 ; weight Z: 0.45 ± 1.14 ; $P = .04$ and $.047$, respectively) and no FA groups (BMI Z: 0.99 ± 1.17 ; weight Z: 0.58 ± 1.12 ; $P = .003$ and $.007$ respectively) as seen in Table I and Fig 1, B. There was no significant difference in height Z score among groups.

The average BMI Z score of the IgE FA subset was normal, although their weight and height Z scores were significantly below 0 (1 sample t test, $P = .02$ and $P < .001$, respectively) (Table I, Fig 1, B). Of these 42 children, 1 (2%) was classified as failure to thrive (defined by BMI < 5th percentile) and 11 (26%) had short stature (height $\leq$ 5th percentile) (see Table E3 in this article's Online Repository at www.jacionline.org). In contrast, the average BMI Z scores in both the skin only and no FA groups were significantly above 0 ($P = .03$ and $P < .001$, respectively). In fact, 3 of 10 (30%) of the skin only group and 12 of 25 (48%) of the no FA groups were overweight (BMI

TABLE I. Characteristics of study participants

	Skin only	IgE FA	No FA	P value (unadjusted)
No.	10	42	25	
Age (y)	8.4 ± 3.6	9.7 ± 4.6	10.3 ± 3.6	.47
Male	6	30	10	.04
BMI, Z score	0.77 ± 1.07	0.08 ± 0.98	0.99 ± 1.17	.003
Height, Z score	-0.27 ± 1.07	-0.81 ± 1.31	-0.42 ± 1.40	.35
Weight, Z score	0.45 ± 1.14	-0.42 ± 1.12	0.58 ± 1.12	.002
SCORAD	51 ± 16	46 ± 16	41 ± 15	.18
Total IgE (IU/mL)	$14,931 \pm 22,962$	$15,220 \pm 16,262$	$9645 \pm 18,178$	.96
Peripheral eosinophil count, no./mm ³	89 ± 263	28 ± 143	20 ± 92	.47
Allergic rhinitis	10	37	23	.64
Asthma	6	34	10	.002
Eosinophilic esophagitis	0	4	0	.26
Steroid use	8	26	19	.53
Immunomodulator use	2	8	6	.92
Percentage of life with eczema	93 ± 5	90 ± 21	82 ± 22	.21

Continuous variables are listed as the mean $\pm$ SD. Unadjusted comparisons were made using ANOVA for continuous variables and Fisher exact for dichotomous variables.

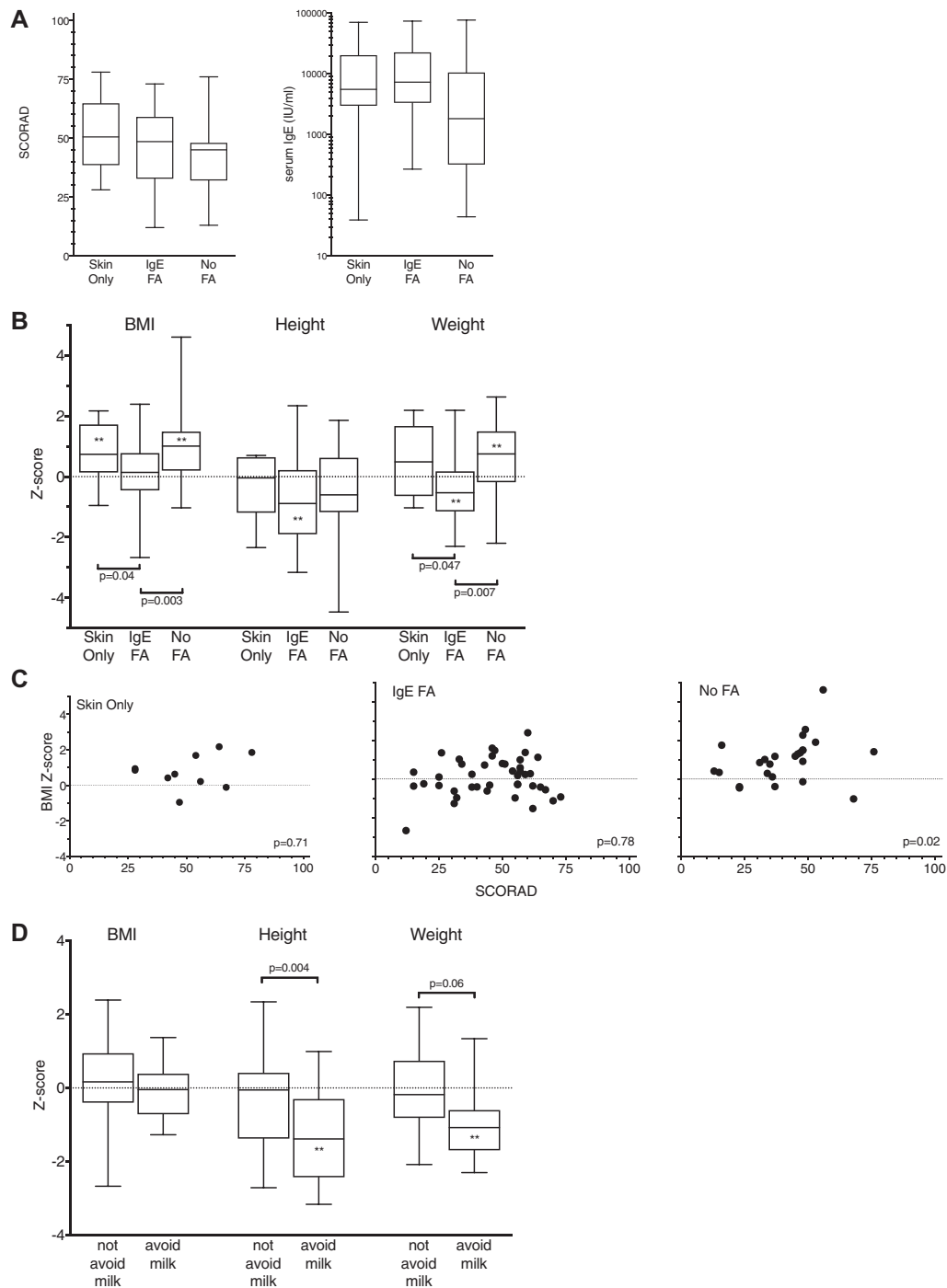


FIG 1. Growth, clinical parameters, and serological measurements of children with moderate-severe AD according to FA status. **A**, SCORAD and total serum IgE measurements in the patient subgroups. **B**, BMI, height, and weight Z scores; *P* values obtained by comparison using linear regression adjusting for age, sex, asthma, and EoE. **C**, Relationship between BMI Z score and SCORAD; *P* value obtained by Spearman correlation. **D**, BMI, height, and weight Z scores in subjects with IgE-mediated FA who were avoiding versus not avoiding milk. *P* values obtained by comparison using linear regression adjusting for age, sex, asthma, and EoE. Double asterisks (**) indicate that measurement is significantly different than 0 by 1 sample *t* test. In the box plots, the box extends from the 25th to 75th percentile with the center line located at the median. The whiskers extend from the minimum to the maximum.

between the 85th and 95th percentiles) or obese (BMI $\geq$ 95th percentile), compared with 7 of 42 (16%) in the IgE FA group (Table E3). The average weight Z score of those with no FA was also significantly above 0 ($P = .02$) (Table I, Fig 1, B). The average height Z scores of the skin only and no FA groups were

not significantly different than 0 (Table I, Fig 1, B), although 2 of 10 (20%) in the skin only group and 3 of 25 (12%) in the no FA group had short stature (Table E3). While AD severity as measured by SCORAD was not associated with BMI Z score in the skin only or IgE FA groups, there was a significant positive

relationship between SCORAD and BMI Z score in children with AD and no FA (Spearman correlation: $P = .02$) (Fig 1, C).

Prior studies have suggested that children with milk allergy are at particularly high risk for growth impairment compared with other types of FA.^{4,5} We therefore compared the growth of children within the IgE FA group who were avoiding milk due to the occurrence of reactions when they consumed milk ($n = 18$) with the growth of those who were not avoiding milk ($n = 24$), adjusting for sex, age, asthma, and EoE. While we observed no difference in BMI Z scores between those avoiding and not avoiding milk, the height Z scores in the milk avoidance group (-1.32 ± 1.25) were significantly lower than those in the not avoiding milk group (-0.43 ± 1.24 , $P = .004$) (Fig 1, D), and a similar trend was seen for weight Z score (-0.92 ± 1.01 vs. -0.05 ± 1.07 , respectively; $P = .06$) (Fig 1, D). The height and weight Z scores of the children avoiding milk were significantly below 0 ($P < .001$ and $P = .001$, respectively); this was not the case for the children who were not avoiding milk (Fig 1, D). The severity of AD (as measured by SCORAD), prevalence of comorbidities (asthma, allergic rhinitis), and steroid use were not significantly different between children who were avoiding milk and those not avoiding milk. We did not find significant differences in BMI, height, or weight Z scores when comparing children within the IgE FA cohort who were avoiding 1 versus 2 or more foods or those who were avoiding egg, soy, wheat, or peanut versus those who were not avoiding these foods (data not shown).

Our data suggest that children with comorbid AD and IgE FA are at significant risk for growth deficiency, particularly if they are avoiding milk. Although the BMI of these subjects was often normal, weight and height Z scores were low. While failure to thrive was not common, over a quarter of this group had short stature. Although those in the skin only cohort were also avoiding major food allergens, these subjects did not show the same impairment in growth, suggesting that food avoidance alone may not entirely account for these observations.

Remarkably, children with moderate-severe AD alone (no FA group), as well as those in the skin only category, were more likely to have an elevated BMI and weight. This is in contrast to a number of prior studies evaluating the growth of children with AD that reported reduced weight and/or stature in AD patients; however, none of these studies controlled for the presence of coexistent FA, although 1 study found that weight and height Z scores of children with eczema decreased as the number of food sensitizations increased.³ Our findings are in keeping with recent studies demonstrating that obesity in early childhood is associated with higher rates of eczema, as well as with more severe disease.⁸ A recent meta-analysis additionally found a positive association between overweight/obesity and increased prevalence of AD, although most studies evaluated were cross-sectional.⁹ We also saw a positive correlation between SCORAD and BMI in the no FA subjects. Importantly, there were no significant differences in AD severity or duration of disease across the 3 groups of children stratified by their food allergic status.

Our study has several important limitations. Cases of IgE FA were not confirmed by oral food challenges. Although AD severity and use of systemic steroids/immunomodulators were not different across the 3 groups, we did not have detailed information regarding overall duration of steroid exposure, which

may independently affect growth. Significant differences between the skin only and IgE FA groups were detected; however, the sample size of the skin only cohort was small, and additional validation of these findings is needed.

In summary, the growth of children with AD may be significantly impaired by the simultaneous presence of IgE FA, particularly milk allergy. In contrast, patients with moderate-severe AD alone are often more likely to have elevated BMI and weight. These data suggest that all children with moderate-severe AD may benefit from close nutritional follow-up. Additional studies are needed to better understand the effects of AD in the presence and absence of FA on metabolism and growth.

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METHODS

Patient characteristics

Subjects 2 to 20 years of age with moderate-severe AD were enrolled in the Natural History of Atopic Dermatitis protocol at the National Institutes of Health. This study was approved by the institutional review board and subjects underwent informed consent and assent, where applicable. Subjects with AD secondary to a known genetic disorder were excluded from the study.

The presence of FA to the 5 most common food allergens (milk, egg, soybean, wheat, and peanut) was determined by a detailed clinical history (via clinic visit and/or phone interview) along with review of clinical records and lab results. To be diagnosed with FA, subjects had to have a convincing history of an immediate hypersensitivity reaction to the food along with positive food-specific IgE testing. A subset of the subjects (1 with possible milk, egg, or wheat allergy; 4 with possible soy allergy; and 20 with possible peanut allergy) were never exposed to the food but were avoiding it because of positive IgE testing. Unfortunately, specific IgE cutoffs that predict likely FA are not well-established in patients with moderate-severe AD,^{E1,E2} and decisions regarding the allergic status of these subjects were empirically determined as follows. The subject with possible milk allergy had a milk-specific IgE level of 74.9 kU_A/L and was counted as milk allergic; the subject with presumed egg allergy had an egg-specific IgE level of 32.6 kU_A/L and was counted as egg allergic; the subject with presumed wheat allergy had a wheat-specific IgE of 43.6 kU_A/L and was counted as wheat allergic. The 4 subjects with possible soy allergy had soy-specific IgE values of 2.5, 12.1, 13.5, and 15.1 kU_A/L and all were classified as nonallergic to soy. Among those avoiding peanut because of positive peanut-IgE testing, 2 had peanut-specific IgE values < 32 kU_A/L and were considered nonallergic to peanut; the remaining had peanut-specific IgE levels ranging from 55 to >100 kU_A/L and were classified as peanut allergic.

Six subjects were regularly eating multiple servings of baked egg and/or milk (but not straight egg or milk) and were classified as nonallergic to milk and egg (they did not report symptoms following ingestion of more concentrated forms of milk and/or egg). Subjects who reported that ingestion

of at least 1 food caused worsening of their AD, while other food(s) caused an immediate IgE-type reaction, were categorized as IgE FA for the group analyses. Skin only subjects did not report acute reactions to any foods—only delayed worsening of their eczema with ingestion of 1 or more foods on multiple occasions. Sensitization to foods were not routinely measured in either the skin only or the no FA groups as they did not report clinical symptoms consistent with an IgE-mediated reaction, and food-specific IgE testing was found to have low positive predictive values in children with late eczematous reactions to foods.^{E3}

Asthma was defined as doctor diagnosis of asthma determined by review of medical records. EoE was defined by the presence of more than 15 eosinophils per high-powered field on esophageal biopsies. Subjects were considered to have been treated with steroids (oral) or immunomodulators if they received these medications at any time during their lifetime as a treatment for AD. In the skin only group, 1 subject received mycophenolate mofetil and 1 subject received methotrexate, cyclosporine, mycophenolate mofetil, and omalizumab. In the IgE FA group, 5 subjects received cyclosporine, 1 subject methotrexate, 1 subject omalizumab, and 1 subject cyclosporine, methotrexate, and omalizumab. In the no FA group, 1 subject received AN2728 phosphodiesterase-4 inhibitor, 1 subject mycophenolate mofetil, 1 subject cyclosporine, 2 subjects cyclosporine and methotrexate, and 1 subject cyclosporine and mycophenolate mofetil.

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TABLE E1. Number of subjects avoiding each food

Avoiding	Skin only	IgE FA
Cow's milk	5 (50)	18 (43)
Egg	5 (50)	24 (57)
Wheat	4 (40)	7 (17)
Soybean	3 (30)	13 (31)
Peanut	6 (60)	39 (93)
Avoiding 2 or more foods	6 (60)	30 (71)

Values are no. (%).

TABLE E2. Duration of food avoidance

	Skin only		IgE FA	
	n/n	Percentage of life	n/n	Percentage of life
Cow's milk	3/5	67 (45-83)	18/18	90 (70-96)
Egg	4/5	52 (39-65)	22/24	88 (75-93)
Wheat	2/4	85 (78-93)	5/7	70 (67-87)
Soybean	3/3	100 (90-100)	10/13	89 (46-98)
Peanut	6/6	97 (72-100)	38/39	100 (77-100)

Median percentage of lifetime that each food was avoided (25th and 75th percentiles in parentheses). Only subjects where the date that avoidance was begun was known were used for the calculation (listed as number for which data is available/total number avoiding that food).

TABLE E3. Number of subjects classified as FTT, overweight, obese, and short stature

	FTT	Overweight	Obese	Short stature
Skin only	0 (0)	0 (0)	3 (30)	2 (20)
IgE FA	1 (2)	6 (14)	1 (2)	11 (26)
No FA	0 (0)	7 (28)	5 (20)	3 (12)

Failure to thrive (FTT) defined as BMI less than the 5th percentile (Z score < -1.645), overweight as BMI between the 85th and 95th percentiles ($1.036 \leq Z$ score < 1.645), and obese as BMI ≥ 95 th percentile (Z score ≥ 1.645). Short stature defined as height ≤ 5 th percentile (Z score ≤ 1.645). Values are no. (%).