

Persistent Food Allergy and Food Allergy Coexistent with Eczema Is Associated with Reduced Growth in the First 4 Years of Life



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What is already known about this topic? Food allergy has previously been associated with lower weight and height in cross-sectional studies in children; however, the presence of coexisting eczema has not been examined, and there have been no longitudinal studies.

What does this article add to our knowledge? We showed that food allergy coexistent with eczema is associated with reduced growth in infancy and early childhood, whereas food allergy or eczema alone has less impact on growth parameters.

How does this study impact current management guidelines? Children with concurrent diagnoses of food allergy and eczema in infancy should be closely followed with good eczema management and dietary guidance to ensure optimal growth.

BACKGROUND: Food allergy has been associated with lower weight and height in cross-sectional studies in children; however, this has not been investigated in longitudinal studies to explore

growth over time, and previous studies have not accounted for coexisting eczema.

OBJECTIVE: The objective of this study was to examine the association of IgE-mediated food allergy and eczema with anthropometric measures at 1 and 4 years of age.

METHODS: In the HealthNuts population-based cohort, infants recruited at age 1 year underwent a skin prick test to egg, peanut, and sesame; those sensitized had oral food challenges. Food challenges repeated at 4 years determined food allergy persistence or resolution. Eczema was defined as parent report of eczema diagnosis. Parent-reported weight and height and child health record data were used to calculate age- and sex-adjusted percentiles from World Health Organization charts. Multivariable linear regression models were fitted to examine the effect of food allergy and eczema on weight and height controlling for potential confounders.

RESULTS: Children with both food allergy and eczema at age 1 had lower percentiles for mean weight (51.3 vs 58.3 percentile, $P = .001$) and height (48.4 vs 53.4, $P = .028$) at age 1 compared with those with neither condition. There was no difference for children with only food allergy or eczema at age 1. By age 4, children with persistent food allergy and persistent eczema, but not those with resolved food allergy, were still shorter and lighter.

CONCLUSIONS: Children with both food allergy and eczema were shorter and lighter throughout early childhood, with more pronounced differences in those with persistent food allergy. © 2015 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2016;4:248-56)

Key words: Food allergy; Eczema; Growth; Infants; Weight; Height; Body mass index

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Abbreviations used

BMI- Body mass index
CMA- Cow's milk allergy
OFC- Oral food challenge
SPT- Skin prick test
WHO- World Health Organization

IgE-mediated food allergy has the potential to affect growth due to the strict elimination diets that are the mainstay of management of this potentially fatal condition. Food allergy is common in infancy, which is a critical growth period.¹ Poor growth in infancy and early childhood has ongoing consequences for children including increased risk of poor cognitive and behavioral development.²

Previous cross-sectional studies have reported an association between food allergy and weight, height, or body mass index (BMI) in children. These have been mostly small studies of less than 100 participants, recruited from tertiary allergy centers,³⁻⁷ and showed current food allergy to be associated with lower weight,^{4,6,7} underweight,^{3,5} and stunting.⁵ Certain groups seem more affected, particularly those with cow's milk^{8,9} or multiple allergies.³ A few large studies have recently been published⁸⁻¹¹ showing that children with some types of food allergy have lower weight, height, and BMI than those without; however, only 2 of these were population representative, and none used the gold standard of oral food challenge (OFC) to diagnose food allergy. Strikingly, there has not been a previous longitudinal study of growth outcomes in food allergic children. The effect of resolution of food allergy on growth outcomes is therefore not known. Resolution of food allergy is likely to influence nutritional status, but no data are available to determine to what extent this may lead to catch-up growth in previously allergic children.

In addition, food allergy is often coexistent with eczema with up to 50% of children with severe eczema also affected by food allergy.¹² Eczema is associated with itching, sleep disturbance, and increased metabolism that have all been suggested to affect growth.¹³⁻¹⁵ No previous studies of food allergy and growth measures have determined the contribution of eczema to these associations to identify which of these might be the major factor impacting on growth and to see whether eczema and food allergy have an additive impact on growth.

It is important to fully investigate any association of food allergy, eczema, and poor growth to be able to identify which children are most at risk so that improved surveillance and nutritional counseling can be offered to these families. Therefore, the aim of this study was to investigate early childhood growth over time in children with persistent and resolving food allergy, with and without eczema compared with children who never had an allergy. The HealthNuts study¹ is ideally placed to investigate this question as it is a large population-representative cohort that has collected anthropometric and challenge-proven food allergy data on children at age 1 and 4 years. We specifically aimed to examine: (1) associations of food allergy and eczema at 1 year of age with anthropometric measures (a) cross-sectionally at 1 year and (b) longitudinally at 4 years of age, and (c) differences between types and numbers of food allergies; (2) associations of food allergy and eczema resolution and persistence by age 4 with growth parameters at age 4 years.

METHODS

Study design, participants, and procedures

The HealthNuts study is a population-representative longitudinal cohort study of 5276 children recruited at age 1 and followed up at age 4. Recruitment has been described in detail previously.¹ Briefly, 12-month-old infants (eligible between 11 and 15 months) were recruited from immunization clinics around Melbourne, Australia, from 2007 to 2011. At recruitment, they underwent skin prick testing (SPT) to egg, peanut, and sesame with a positive control (histamine 10 mg/mL) and negative control (saline) using single-tine lancets on the child's back. They were also examined for eczema, and parents completed a questionnaire.

All children with a detectable wheal on SPT (≥ 1 mm) were invited to attend the clinic at the Royal Children's Hospital. SPTs were repeated and all then underwent an OFC, unless they had experienced a reaction in the previous 2 months consistent with OFC stopping criteria. OFCs were administered by staff blinded to the SPT wheal size and clinical history, as previously described.¹⁶

At age 4, all parents were asked to complete another questionnaire, and children who had food allergy at age 1 underwent repeat SPT, OFC, and height and weight measurements in a clinic assessment.¹⁷

Measures

Exposure variables

Food allergy definitions. Food allergy at age 1 was defined as positive SPT and positive OFC to egg, peanut, or sesame. OFC was defined as positive if the following criteria were met within 2 hours of the final challenge dose: 3 or more concurrent noncontact urticarial reactions lasting 5 minutes or more, angioedema, vomiting, or evidence of anaphylaxis (circulatory or respiratory compromise). Presumed IgE-mediated cow's milk allergy (CMA) was also included in the food allergy definition at age 1, estimated by parent report of acute reaction to dairy (<1 hour after ingestion). Presumed non-IgE-mediated CMA was investigated separately and defined as parent report of delayed reaction to dairy (>1 hour after ingestion).

Persistent food allergy was defined as a positive food challenge or parent report of reaction in the previous 2 months consistent with IgE-mediated symptoms at age 4 in those with a positive challenge at age 1. Resolved food allergy was defined as a challenge-proven allergy at age 1, and tolerant on challenge at age 4 years.¹⁷

Eczema definitions. Eczema at age 1 year was defined as parent report of doctor-diagnosed eczema within the first year of life or eczema observed on the face, back, or elbow flexures by a trained nurse at the time of recruitment. Persistent eczema was defined as eczema at age 1 year and eczema at age 4 years (with symptoms in the last 12 months). Resolved eczema was defined as eczema at age 1 and not current at age 4 (no symptoms in the last 12 months).

Outcome variables: anthropometric measures. Weight and length measurements at birth and most recent weight and length measurements and date of measurement for age 1 were reported by parents in the age 1 questionnaire as recorded in their Child Health Record by their maternal child health nurse. Age 4 height and weight measurements recorded in the clinic were used when available; otherwise, parent-reported values from the questionnaire were used.

Height, weight, sex, and age were used to calculate age- and sex-adjusted *z* scores and percentiles for height, weight, and BMI based

TABLE I. Characteristics of HealthNuts participants included in analysis at age 1 or 4 years or both or excluded from all analyses

	Included at both ages 1 and 4 n† = 1183	Included at age 1 n† = 2721	Included at age 4 n† = 1658	Excluded from all analysis n† = 2080
Family characteristics*				
Family history of allergy (%)	74.6	71.1	74.0	66.5
Both parents born in Australia (%)	67.9	63.4	66.6	52.3
Maternal smoking during pregnancy (%)	2.1	3.9	2.0	6.5
Socioeconomic quintile (%)				
1 (most disadvantaged)	14.0	18.4	14.6	23.6
2	20.5	20.0	21.8	18.7
3	23.2	21.7	22.1	20.4
4	22.6	20.4	21.9	17.8
5 (least disadvantaged)	19.7	19.6	19.6	19.5
Any siblings (%)	48.6	49.2	48.8	52.2
Pet dog (%)	32.2	31.5	32.2	32.2
Infant characteristics*				
Sex: male (%)	50.0	49.9	51.5	51.1
Mode of delivery: vaginal (%)	66.2	66.9	66.4	66.6
Preterm (%)	5.4	6.1	5.6	6.4
Birthweight (g, mean)	3434.6	3397.3	3432.4	3378.6
Eczema history: by 12 mo (%)	28.3	26.3	27.1	27.8
Duration of any breast feeding (months, mean)	10.6	9.7	10.4	9.1
Age at intro to solids (months, mean)	5.6	5.7	5.6	5.7
Formula use (%)				
Cow's milk formula	57	61	58.8	66.8
Partially hydrolyzed formula	10.8	10.9	10.9	9.5
Soy formula	1.3	1.3	1.0	1.4
Extensively hydrolyzed/amino acid formula	0.6	0.6	0.8	1.0
Other	3.9	3.6	3.5	4.4
No formula	26.3	22.6	25	16.9
IgE-mediated food allergy to peanut, sesame, or egg (%) at 1 y	14.9	11.7	14.4	9.2
Presumed IgE-mediated cow's milk allergy in first year (%)	3.9	3.2	3.6	3.3
Presumed non-IgE-mediated cow's milk allergy in first year (%)	3.8	3.0	3.7	2.9

*Variables in this table were tested as potential confounders for the linear regression models.

†n is maximum in each category when restricted to those with information on weight, height, sex, birthweight, eczema status, duration of breastfeeding, socioeconomic indexes for areas quintile, parent's country of birth, and food allergy status at age 1. Other variables may have some missing data.

on the World Health Organization (WHO) growth charts.¹⁸ Biologically implausible *z* scores were excluded from analysis (accepted range for weight: −6 to +5, height: −6 to +6, and BMI: −5 to +5). Height and weight measurements were excluded if recorded outside 9 to 15 months for the age 1 data point, and outside 3 to 5 years for the age 4 data point, or if height and weight were recorded over 1 month apart.

Statistical analysis

Associations between exposure and outcomes were analyzed using multivariable linear regression (for continuously valued outcomes) or multivariable logistic regression (for binary outcomes). There was evidence that the relationship between food allergy and growth differed by eczema status (*P* for interaction at age 1 for weight = .018, height = .048, BMI = 0.080); therefore, eczema was considered in combination with food allergy status for all analyses.

For all regression analyses, birth weight, prematurity (gestation <37 weeks), socioeconomic index (socioeconomic indexes for areas quintiles), and parent's country of birth (both Australian, one European, both European, one east Asian, both east Asian, or other) as

a proxy measure of ethnicity were *a priori* selected as known confounders. Other potential confounders (age 1: age, gender, family history of allergy, any siblings, pets, mode of delivery, history of eczema, antibiotic use in first year of life, duration of any breastfeeding, age of introduction to solids, history of eczema, and topical corticosteroid usage for eczema; age 4: as for age 1, plus history of asthma, regular use of inhaled steroids) were considered but only retained in the regression model if their individual inclusion changed the estimated regression coefficient for the association between the percentile (weight-for-age, height-for-age, or BMI) and food allergy by more than 10%. Gender and parents country of birth were investigated as effect modifiers by including the interaction term in the model and evaluated using the Wald test.

The association between the presence of food allergy at age 1 and height, weight, and BMI percentiles as continuous variables at both ages 1 and 4 years was quantified with exposure groups defined as no food allergy, no eczema; food allergy, no eczema; no food allergy, eczema; and both food allergy and eczema.

The association between persistent or resolved food allergy and height, weight, and BMI percentiles as continuous variables at age 4

years was quantified with exposure groups defined as combinations of never food allergic, resolved food allergy, and persistent food allergy with never eczema, resolved eczema, and persistent eczema.

To examine whether any differences in growth were clinically relevant, a secondary multivariable logistic regression analysis was used to investigate the association between food allergy and eczema at age 1 on BMI categories of underweight, normal weight, and overweight at ages 1 and 4. The WHO definitions and *z*-score cutoffs were used for these categories: underweight < -2, normal weight from -2 to +2, and overweight > +2.¹⁸

Adjustment for differences in demographic characteristics or other risk factors between included and excluded participants was made using the inverse probability weighting, as described by Little and Rubin.¹⁹ Weights were calculated as the inverse of the probability of inclusion (ie, having a complete dataset) obtained from a logistic regression model of participation. The probability was derived from information available on risk factors for both those included and excluded: family history of allergy, parent's country of birth, mother smoked during pregnancy, socioeconomic index, eczema diagnosis, duration of any breastfeeding, and formula feeding. Stata Version 13.0 (StataCorp, College Station, Tex) was used for all analyses.

Ethics

Ethics approval was obtained from the Office for Children, Department of Human Services, and Royal Children's Hospital Ethics Committees.

RESULTS

Participants were included if complete data were available on weight, height, age, sex, food allergy, and eczema status as well as information on final confounders (birthweight, prematurity, socioeconomic status, parent's country of birth, and duration of any breastfeeding). This information was available for 2721 (51.6%) children at age 1, 1658 (31.4%) at age 4, and 1183 (22.4%) at both 1 and 4 years (flow chart in Figure E1, available in this article's Online Repository at www.jaci-inpractice.org). Table I shows characteristics of children included and excluded from analyses at ages 1 and 4 years.

Association between food allergy and eczema at age 1 and growth parameters at (a) age 1 and (b) age 4

Children with both IgE-mediated food allergy (egg, peanut, sesame, or cow's milk) and eczema at age 1 had lower weight, height, and BMI at age 1 compared with children with neither food allergy nor eczema (Figure 1, A; Table E1, available in this article's Online Repository at www.jaci-inpractice.org). Food allergy or eczema alone was not associated with reduced growth parameters at age 1. At age 4, those with food allergy at age 1 had lower weight and lower height whether or not they also had eczema at age 1, although this only reached significance at the $P < .05$ level for height for those with food allergy alone (Figure 1, B; Table E1). Eczema alone still had no effect. There was no effect modification by gender or parent's country of birth ($P > .05$ for all Wald tests).

At age 1, there were no differences in WHO BMI categories for any group (OR: 1.59, 95% CI: 0.045-5.67, $P = .473$). At age 4, those with food allergy and eczema as infants were more likely to be underweight, according to WHO BMI categories, compared with those with no food allergy or eczema (OR: 2.57, 95% CI: 1.11-5.95, $P = .027$).

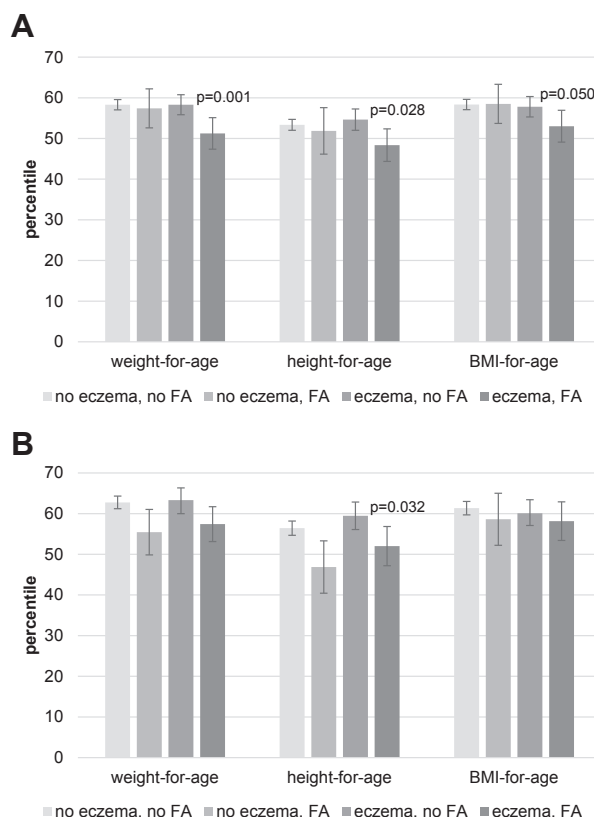


FIGURE 1. Weight-for-age, height-for-age, and BMI-for-age percentiles at (A) age 1 year and (B) age 4 years presented by food allergy and eczema status at age 1 year. *P* values are for comparison to the "no eczema or food allergy" group calculated from multivariable linear regression (Table E1); only those $P \leq .05$ are shown. Error bars represent 95% CI. BMI, Body mass index; FA, food allergy.

To further explore whether the lower weight and height in those with both food allergy and eczema may be due to greater eczema severity in this group, a secondary analysis was conducted that further subdivided those with eczema into mild or severe categories (severe defined as diagnosis before 6 months of age and use of prescription topical steroids). Food allergy was associated with lower growth parameters in those with eczema, irrespective of eczema severity. Eczema alone had no effect on weight or height, whether mild or severe (Table E2, available in this article's Online Repository at www.jaci-inpractice.org).

Types and number of food allergies

Egg, peanut, and presumed IgE-mediated CMA at age 1 were all associated with lower weight and height if eczema was also present (Table E1, available in this article's Online Repository at www.jaci-inpractice.org) at age 1. There was less evidence of an association between food allergy at age 1 and weight or height at age 4. Both egg allergy (OR: 3.77, 95% CI: 1.44-9.87, $P = .007$) and peanut allergy (OR: 3.79, 95% CI: 1.14-12.55, $P = .029$) at age 1 were associated with underweight (WHO BMI categories) at age 4. There was modest evidence that those with presumed non-IgE CMA and eczema were lighter at age 1

TABLE II. Association between food allergy and eczema status at age 1 and height-for-age, weight-for-age, and BMI-for-age z scores at ages 1 and 4*

Eczema status	Food allergy status	Age 1						Age 4					
		Weight-for-age			Height-for-age			Weight-for-age			Height-for-age		
		n	β	P	β	P	BMI-for-age	n	β	P	β	P	BMI-for-age
Multiple IgE food allergy†	No FA	1855			Baseline group			1057			Baseline group		
	1 FA	116	2.652	.265	2.945	.263	1.783	.491	74	-2.030	.489	-1.420	.675
	2 or more FA	21	-6.404	.241	-9.225	.126	-2.883	.627	18	-9.747	.096	-17.26	.011
	No FA	486	1.401	.268	2.511	.073	0.385	.779	273	0.085	.959	2.883	.133
	1 FA	126	-5.976	.009	-6.280	.013	-2.501	.317	87	-2.500	.363	-3.118	.326
	2 or more FA	68	-6.620	.031	-4.837	.155	-4.812	.151	52	-3.402	.332	-1.493	.712
Non-IgE-mediated CMA‡	No CMA	1916			Baseline group			1095			Baseline group		
	Non-IgE-mediated CMA	47	-4.776	.192	-2.588	.523	-4.321	.278	32	-4.221	.335	-9.985	.049
	No CMA	611	-0.205	.860	0.924	.471	-0.586	.642	365	-0.399	.789	1.219	.481
	Non-IgE-mediated CMA	35	-8.111	.055	-3.799	.417	-7.481	.104	27	-8.381	.078	-0.100	.986

BMI, Body mass index; CMA, cow's milk allergy; FA, food allergy.

Bold indicates $P < 0.05$.*Linear regression, showing coefficients (β) and P values reported for a multivariable model including birth weight, prematurity, socioeconomic status, parent's country of birth, and duration of breastfeeding.†Multiple IgE food allergy includes challenge-proven egg, peanut, or sesame allergy and presumed IgE-mediated CMA (estimated from parent report of reaction to milk in the first year of life; reaction < 1 h).‡Presumed non-IgE-mediated CMA is estimated from parent report of reaction to milk in the first year of life with adverse reactions > 1 h after ingestion.

($P = .055$) and age 4 ($P = .078$) and shorter at age 4 in the absence of eczema ($P = .049$) compared with children with no CMA or eczema, but there was little evidence of a difference in other growth parameters (Table II). There were no clear dose-response effects seen in those with increasing numbers of allergy at age 1 (Table II).

Resolved and persistent allergy

At age 4, compared with those who never had a food allergy, those with persistent food allergy have lower weight and height, but not BMI (Figure 2; Table E3, available in this article's Online Repository at www.jaci-inpractice.org). This was seen across all eczema groups, although the weight and height were lowest in those with both persistent food allergy and persistent eczema at age 4 (Table E3). At age 4, there was no evidence of a difference in weight or height for those children with resolved food allergy compared with those who never had a food allergy.

Figure 3 shows the change in weight, height, and BMI from ages 1 to 4 and how this differs by food allergy and eczema status over time. At age 1, differences are apparent only in those with both food allergy and eczema. However, there was a negative gradient in height and weight percentiles for those with food allergy but without eczema between ages 1 and 4 years, so that they were shorter and lighter by age 4. In the persistent eczema group, there appeared to be some catch-up growth between ages 1 and 4 for those with resolved food allergy.

DISCUSSION

This is the first population-based study to investigate the individual and combined effects of food allergy and eczema on longitudinal growth patterns in children. At age 1 year, children with food allergy and coexisting eczema were shorter and lighter than those with neither condition. These differences persisted to age 4 years, although there was evidence of catch-up growth amongst those whose food allergy resolved between ages 1 and 4. Our results indicate that eczema affects early growth in food allergic children, as differences in growth had already occurred by age 1, whereas in those with food allergy without eczema growth is affected later, with no differences at age 1 but lower weight and height by age 4. We also found that those with food allergy at age 1 were more likely to be underweight according to WHO BMI categories at age 4.

The major strengths of this study are in its design as a large population-representative prospective cohort study. In addition, the use of OFC-proven food allergy definitions at both ages allowed for accurate diagnosis and assessment of resolution or persistence of food allergy. We collected data on important potential confounders that were considered in the relationship between food allergy and growth. For the first time, eczema was considered in conjunction with food allergy and was found to be an important modifier of the effect of food allergy on growth, especially at age 1.

A limitation of this study is that weight and height at age 4 were primarily parent reported that may result in inaccuracies. Biologically implausible weight, height, or BMI z scores were excluded, a technique that is often used to minimize errors in anthropometric measures.²⁰ Remaining errors are likely to be random errors²¹; therefore, we may be underestimating growth parameter differences. Eczema was defined as report of doctor-diagnosed eczema. SCORAD (SCORing Atopic Dermatitis), which would allow for defining eczema severity more objectively,

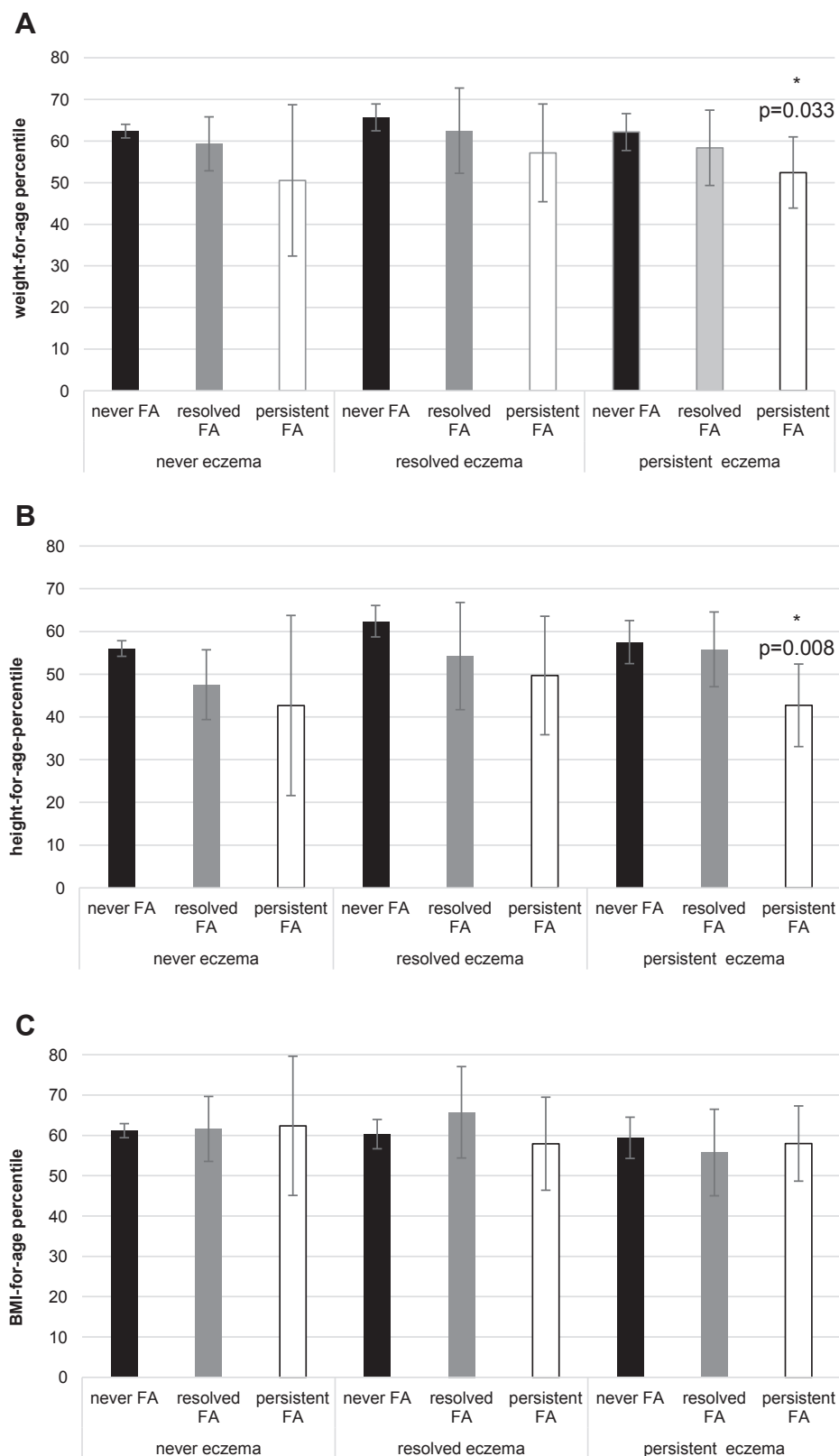


FIGURE 2. **A**, Weight for age; **B**, height for age; and **C**, BMI for age percentiles at age 4, for those never allergic, with resolved food allergy (positive OFC age 1 years, negative age 4 years) and persistent food allergy (positive OFC at age 1 and 4 years), presented by eczema status. *P* values are for comparison to the “never food allergic, never eczema” group calculated from multivariable linear regression (Table E3); only those *P* < .05 are shown. Error bars represent 95% CI. *BMI*, Body mass index; *FA*, food allergy; *OFC*, oral food challenge.

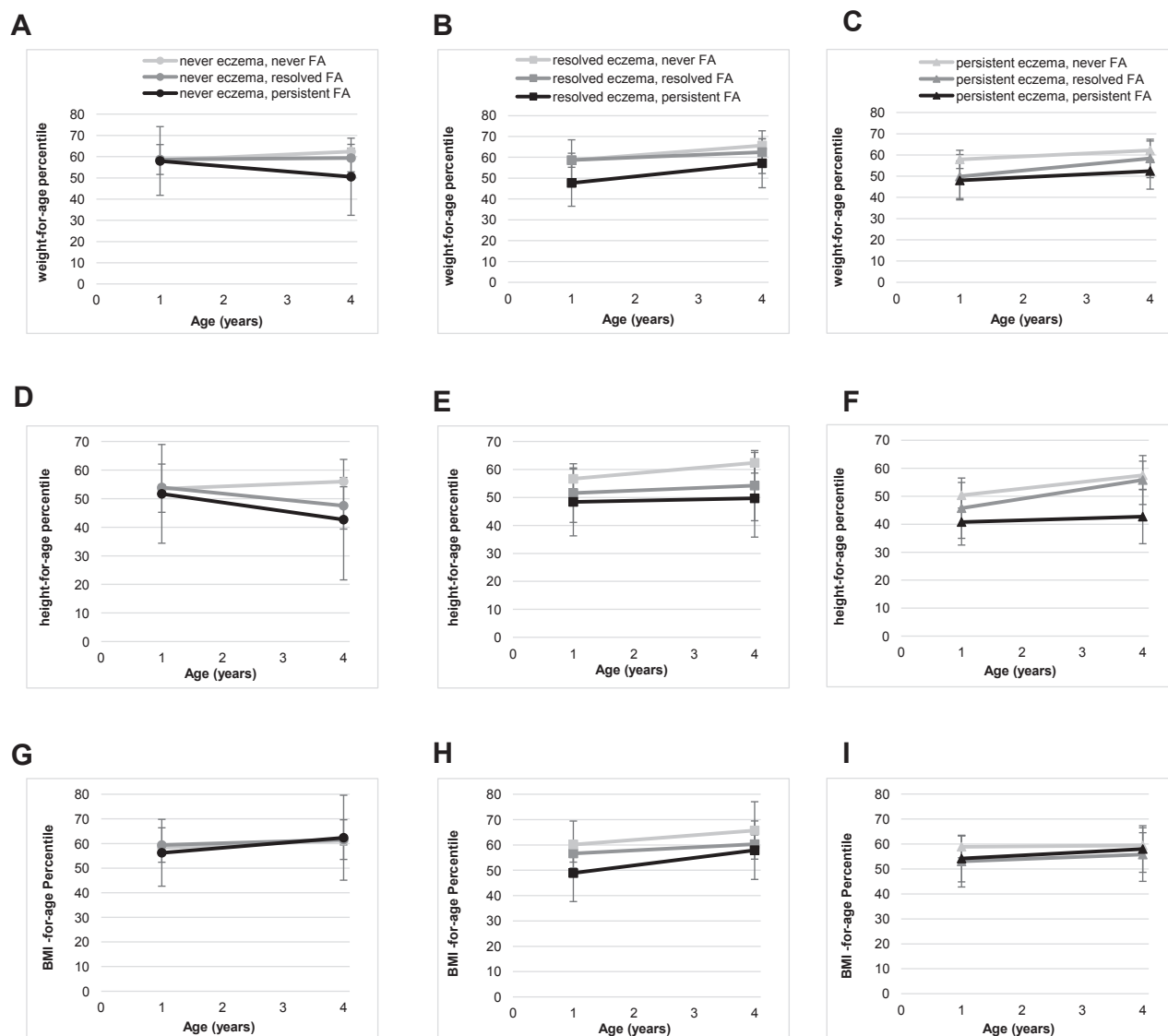


FIGURE 3. Growth trajectories of children with and without eczema presented by never allergic, resolved food allergy, and persistent food allergy over the first 4 years of life. **A**, Weight-for-age without eczema. **B**, Weight-for-age with resolved eczema. **C**, Weight-for-age with persistent eczema. **D**, Height-for-age without eczema. **E**, Height-for-age with resolved eczema. **F**, Height-for-age with persistent eczema. **G**, BMI-for-age without eczema. **H**, BMI-for-age with resolved eczema. **I**, BMI-for-age with persistent eczema. Error bars represent 95% confidence intervals. *BMI*, body mass index; *FA*, food allergy.

was not used; however, eczema severity using a proxy measure did not appear to affect our results. Another limitation is missing height and weight data both at ages 1 and 4 years. However, when sampling weights were included to account for differences in characteristics in those with and without missing data, our findings were consistent.

A major finding from this study was that food allergy and eczema together in the first year of life had a greater impact on growth parameters than either condition alone. This has not been investigated before, although previous studies showing reduced growth in children with food allergies have suggested that the effect of eczema should be explored.⁶ It is well known that food allergy and eczema often occur together.¹² Although the effect of these conditions on growth has been examined

separately, there have been no studies to report on the combination. Although the reductions in height and weight that we found at the population level were not large, they correlated well with differences seen in previous studies looking at food allergy only. Mehta et al¹¹ found that children with and without food allergies had mean height percentiles of 52.4 and 66.3, respectively, and weight percentiles of 46 and 52.8, respectively. Similarly, Mukaida et al¹⁰ found those that avoided foods in infancy were less likely to be overweight but not more likely to be underweight when assessed at school age.

We did not note any differences in growth due to eczema only. Eczema has been shown to be associated with reduced weight¹⁵ and height¹³ in some studies, and this difference is predominantly restricted to those with severe eczema.^{14,22} It may

be that these previous studies have captured children with concurrent food allergy and eczema. The only study investigating the effect of food sensitization on growth in a group of children with eczema found that, as the number of allergen sensitizations increased, the weight and height *z* scores decreased.¹⁴

We did not find a dose-response effect of the number of food allergies on growth parameters, which is similar to a large retrospective study investigating the effect of food allergy only on growth.¹¹ Most studies that have found a dose-response relationship between number of allergies and growth deficiencies have been smaller, case-matched studies of children recruited from tertiary allergy centers that may represent a more severe atopic group.^{3,5}

We found that IgE-mediated CMA with eczema had a similar mildly negative effect on growth parameters to egg and peanut allergy at age 1. Non-IgE CMA at age 1 also resulted in lower magnitude of growth parameters and was also associated with more children being underweight according to WHO BMI categories at both ages 1 and 4. Previous studies have consistently found that CMA is associated with lower growth parameters,^{8,11,23} but these have usually been in older children with persistent CMA and often include a combination of IgE and non-IgE milk allergy. Mehta et al¹¹ reported that although milk allergy was associated with reduced growth in older age groups, in those under 2 years there was no effect. This is perhaps explained by adequate replacement of milk by hypoallergenic formula in the first 2 years of life and may be why our results do not show as large an effect as some other studies.

The investigation of the effect of resolved and persistent food allergy is another key feature of this study. Those with persistent food allergy at age 4 were shorter and lighter at age 4, whereas those with resolved allergy were not, even though as a group at age 1, they all had lower growth parameters. Although no other prospective, longitudinal studies have been conducted investigating growth and persistent or resolved food allergy, Mukaida et al¹⁰ estimated this effect by retrospectively asking when children who avoided foods in infancy grew out of their food allergy. Those who had food allergy for longer and especially those who had persistent allergy at age 6 had lower weight when assessed at ages between 7 and 15 years, which is consistent with our results.

It is plausible that the mechanism for reduced growth parameters in children with food allergies is poor dietary intake due to exclusion diets, and this is the most commonly cited hypothesis. This is most plausible for foods such as cow's milk and wheat that make up significant proportion of an infant's diet. However, in our study, foods that are not of high nutritional importance such as peanut were also associated with reduced growth. Therefore, this reduced growth is potentially due to an atopic phenotype and may be mediated by the effect of chronic allergic inflammation and increased metabolic demands.⁹ Eczema has been hypothesized to impact growth via increased metabolic demands associated with itch, sleep disturbance, and increased skin turnover.¹³ The apparent combined effect on growth of food allergy and eczema seen in this study may be explained by these children exhibiting a more severe allergic phenotype.

In conclusion, we found that in a population-based cohort, children with eczema and food allergy at age 1 were shorter and lighter throughout early childhood than children with neither condition. This is particularly so for those with persistent food allergy at 4 years. These results emphasize the need for adequate nutritional follow-up for all food allergic infants, not just those

with allergies to nutritionally important foods, and particularly for those with eczema.

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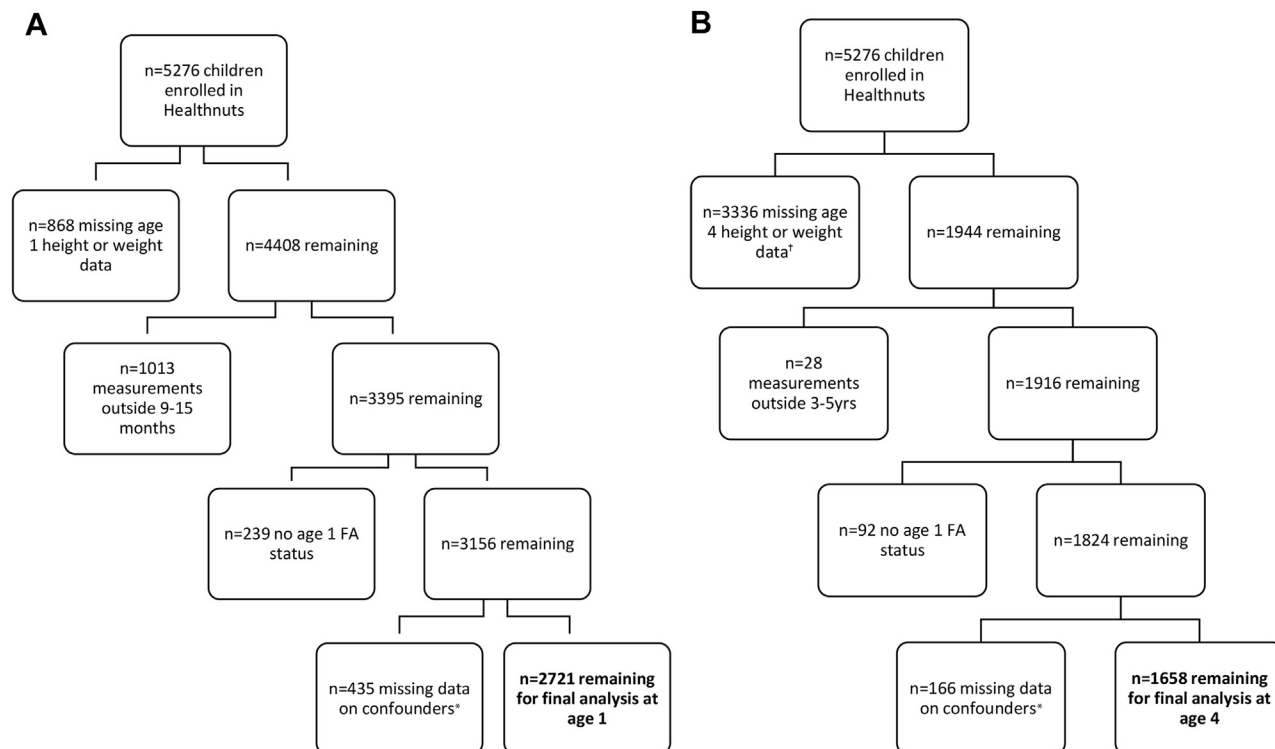


FIGURE E1. Flow chart of participants included at **(A)** age 1 and **(B)** age 4. *Confounders: birth weight, prematurity, socioeconomic index, parent's country of birth, duration of any breastfeeding. †Of these, n = 1025 did not respond to any questionnaire or could not be contacted, n = 1163 responded to the short questionnaire that did not collect height and weight data, and n = 1148 did not fill in height and weight data on the full questionnaire.

TABLE E1. Association between food allergy and eczema status at age 1 and height-for-age, weight-for-age, and BMI-for-age z scores at ages 1 and 4 *

	Eczema status§	Food allergy status	n	Age 1						Age 4					
				Weight-for-age		Height-for-age		BMI-for-age		Weight-for-age		Height-for-age		BMI-for-age	
				β	P	β	P	β	P	β	P	β	P	β	P
Any FA†	No eczema	No FA	1888	Baseline group						1080	Baseline group				
	No eczema	FA	119	0.531	.821	−1.067	.681	1.876	.463	82	−4.221	.133	−6.957	.032	−0.893 .781
	Eczema	No FA	514	0.897	.467	2.061	.132	0.101	.940	287	0.324	.842	2.901	.124	−1.535 .408
	Eczema	FA	200	−5.916	.001	−4.544	.028	−3.968	.050	144	−3.093	.160	−2.650	.298	−1.758 .484
Egg allergy	No eczema	No egg allergy	1903	Baseline group						1091	Baseline group				
	No eczema	Egg allergy	102	0.103	.967	−0.108	.969	1.001	.716	69	−3.565	.242	−6.382	.070	−0.704 .840
	Eczema	No egg allergy	530	0.761	.532	1.926	.154	0.037	.978	302	0.166	.917	3.003	.103	−1.832 .314
	Eczema	Egg allergy	179	−6.526	.001	−4.782	.027	−4.563	.032	127	−3.243	.163	−3.825	.155	−0.909 .732
Peanut allergy	No eczema	No peanut allergy	1978	Baseline group						1140	Baseline group				
	No eczema	Peanut allergy	29	2.184	.638	−4.179	.416	4.072	.419	22	−7.440	.156	−12.44	.040	1.253 .834
	Eczema	No peanut allergy	640	−0.141	.901	0.650	.604	−0.234	.849	372	−0.274	.852	1.653	.330	−1.139 .496
	Eczema	Peanut allergy	61	−8.052	.013	−3.157	.379	−8.294	.018	52	−1.779	.611	2.398	.553	−4.928 .217
Sesame allergy	No eczema	No sesame allergy	2004	Baseline group						1161	Baseline group				
	No eczema	Sesame allergy	3	−17.20	.229	−4.722	.766	−20.38	.190	1	−26.02	.286	−46.53	.100	20.94 .452
	Eczema	No sesame allergy	687	−1.203	.275	0.405	.740	−1.468	.220	412	−0.651	.645	1.530	.351	−1.751 .278
	Eczema	Sesame allergy	21	3.198	.556	−3.119	.605	6.684	.258	16	7.742	.208	7.697	.279	5.577 .426
IgE-mediated cow's milk allergy‡	No eczema	No CMA	1916	Baseline group						1095	Baseline group				
	No eczema	IgE-mediated CMA	31	−3.026	.500	0.302	.952	−4.755	.330	24	−9.216	.068	−6.673	.255	−10.06 .080
	Eczema	No CMA	611	−0.266	.818	0.895	.485	−0.643	.609	365	−0.399	.789	1.219	.481	−0.925 .586
	Eczema	IgE-mediated CMA	35	−5.710	.096	−7.436	.049	−0.839	.822	30	−1.497	.741	−3.265	.534	−2.441 .635

BMI, Body mass index; CMA, cow's milk allergy; FA, food allergy.

Bold indicates $P < 0.05$.

*Linear regression, showing coefficients (β) and P values reported for a multivariable model including birth weight, prematurity, socioeconomic status, parent's country of birth, and duration of breastfeeding.

†Any IgE-mediated food allergy includes challenge-proven egg, peanut, or sesame allergy and IgE like cow's milk allergy (estimated from parent report of reaction to milk in the first year of life, reaction < 1 h).

‡IgE-mediated cow's milk allergy is estimated from parent report of reaction to milk in the first year of life, with a reaction < 1 h.

§Eczema is defined as eczema status at age 1 year.

TABLE E2. Association between food allergy and eczema severity at age 1 with weight, height, and BMI percentiles at age 1

Eczema, food allergy status at age 1	n	Age 1					
		Weight-for-age*		Height-for-age*		BMI-for-age*	
		β	P	β	P	β	P
No eczema, no food allergy	1888	Baseline group					
No eczema, food allergy	119	0.541	.817	−1.029	.691	1.860	.464
Mild eczema, no food allergy	191	0.646	.729	1.514	.466	−0.487	.811
Mild eczema, food allergy	82	−9.390	.001	−4.920	.113	−8.633	.005
Severe eczema, no food allergy	61	−1.230	.702	1.161	.745	−2.225	.524
Severe eczema, food allergy	56	−5.132	.126	−4.208	.258	−3.148	.388

BMI, Body mass index.

Bold indicates $P < 0.05$.

*Linear regression, showing coefficients and P values, for a multivariable model including birth weight, prematurity, socioeconomic index, parent's country of birth, and duration of breastfeeding.

TABLE E3. Association of resolved and persistent food allergy and eczema status at age 4 with weight, height, and BMI percentiles at age 4

Eczema, food allergy status at age 4	n	Weight-for-age*		Height-for-age*		BMI-for-age*	
		β	P	β	P	β	P
		β	P	β	P	β	P
Never eczema, never FA	990	Baseline group					
Never eczema, resolved FA	47	−0.340	.925	−6.197	.140	1.884	.652
Never eczema, persistent FA	12	−4.822	.496	−7.769	.342	5.955	.464
Resolved eczema, never FA	230	1.766	.323	5.005	.015	−1.812	.377
Resolved eczema, resolved FA	23	0.710	.891	−1.492	.802	4.970	.402
Resolved eczema, persistent FA	20	−4.251	.439	−5.278	.406	−2.819	.655
Persistent eczema, never FA	130	0.144	.949	1.966	.454	−1.728	.508
Persistent eczema, resolved FA	32	−0.962	.827	2.490	.623	−3.931	.435
Persistent eczema, persistent FA	37	−8.725	.033	−12.541	.008	−2.230	.635

BMI, Body mass index; FA, food allergy.

Bold indicates $P < 0.05$.

*Linear regression, showing coefficients and P values, for a multivariable model including birth weight, prematurity, socioeconomic index, parent's country of birth, and duration of breastfeeding.

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