

have implications for immune function. Contrasting reports of the effect of individual glycoforms on IgG function and simultaneous variation across a wide spectrum of glycoforms complicate prediction of the net functional effect of the changes observed here.¹ In healthy children the abundance of digalactosylated and sialylated forms, as well as enhanced core fucosylation, could attenuate the effector potency of the IgG pool, especially before the age of 2 years. Whether the glycan changes noted here in children with unexplained RRI represent a predisposing factor or an effect of frequent infections cannot be determined from this data set. However, chronic immune stimulation is typically associated with lower levels of sialylation, galactosylation, or both, a pattern distinct from and even opposite that observed here.^{3,8,9} If IgG Fc glycan aberrancy predisposes to RRI in some children, then an intriguing implication is that immunoglobulin supplementation addresses not only abundance and repertoire but also the deficit in IgG bearing normal Fc glycans and therefore with normal effector function.

Assessment of IgG Fc glycans is not part of the routine immunologic evaluation. Our data suggest that IgG Fc glycosylation represents an axis of humoral immune regulation in childhood and raise the intriguing possibility that IgG glycan aberrancy could contribute to otherwise unexplained respiratory tract infections in some patients. These findings highlight the need to consider the effect of IgG Fc glycans on immunocompetence in childhood and beyond.

Hao D. Cheng, PhD^a
Irit Tirosh, MD^{b,l}
Noortje de Haan, PhD^c
Henning Stöckmann, PhD^d
Barbara Adamczyk, PhD^d
Ciara A. McManus, PhD^d
Róisín O'Flaherty, PhD^d
Gordon Greville, MSc^d
Radka Saldova, PhD^{d,e}
Francisco A. Bonilla, MD, PhD^b
Luigi D. Notarangelo, MD^f
Gertjan J. Driessen, MD, PhD^{g,h}
Ingrid A. Holm, MDⁱ
Pauline M. Rudd, PhD^d
Manfred Wuhrer, PhD^c
Margaret E. Ackerman, PhD^{a,j}
Peter A. Nigrovic, MD^{b,k}

From ^athe Molecular and Cellular Biology Program and ^jThayer School of Engineering, Dartmouth College, Hanover, NH; ^bthe Division of Immunology and ^cthe Division of Endocrinology, Boston Children's Hospital, Boston, Mass; ^dthe Center for Proteomics and Metabolomics, Leiden University Medical Center, Leiden, The Netherlands; ^ethe Glycoscience Group, National Institute for Bioprocessing Research and Training, Dublin, Ireland; ^fthe College of Health and Agricultural Science, UCD School of Medicine, University College Dublin, Dublin, Ireland; ^gthe Laboratory of Clinical Immunology and Microbiology, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Md; ^hthe Department of Pediatrics, Juliana Children's Hospital, Haga Teaching Hospital, The Hague, The Netherlands; ⁱthe Department of Pediatrics, Erasmus Medical Center, Sophia Children's Hospital, Rotterdam, The Netherlands; ^kthe Division of Rheumatology, Inflammation and Immunity, Brigham and Women's Hospital, Boston, Mass; and ^lRheumatology Unit, Edmond and Lily Safra Children's Hospital, Sheba Medical Center, Israel. E-mail: Margaret.e.ackerman@dartmouth.edu. Or: pnigrovic@bwh.harvard.edu.

L.D.N. was supported by the Division of Intramural Research, National Institute of Allergy and Infectious Diseases, National Institutes of Health. R.S. was supported by funding from the Science Foundation Ireland Starting Investigator Research Grant (SFI SIRG) under grant number 13/SIRG/2164. H.S. and R.O.F. were supported by the funding from EU FP7 Program HighGlycan, grant number 278535. M.E.A. was supported by NIH grants P20GM104416, R01AI131975, and P01AI120756 and an Innovative Research Award from the Rheumatology Research Foundation. P.A.N.

was supported by NIH grants R21AI099435, R01AR065538, R01AR073201, R01AR075906, and P30AR070253; an Innovative Research Award from the Rheumatology Research Foundation; the Cogan Family Foundation; the Fundación Bechara; and the Arbuckle Family Fund for Arthritis Research.

Disclosure of potential conflict of interest: L. D. Notarangelo was supported by the Division of Intramural Research, National Institute of Allergy and Infectious Diseases, National Institutes of Health (NIH). M. E. Ackerman was supported by NIH grants P20GM104416, R01AI131975, and P01AI120756 and an Innovative Research Award from the Rheumatology Research Foundation. P. A. Nigrovic was supported by NIH grants R21AI099435, R01AR065538, R01AR073201, R01AR075906, and P30AR070253; an Innovative Research Award from the Rheumatology Research Foundation; the Arbuckle Family Fund for Arthritis Research; and the Fundación Bechara. The rest of the authors declare that they have no relevant conflicts of interest.

REFERENCES

1. Dekkers G, Rispen T, Vidarsson G. Novel concepts of altered immunoglobulin G galactosylation in autoimmune diseases. *Front Immunol* 2018;9:553.
2. Parekh R, Roitt I, Isenberg D, Dwek R, Rademacher T. Age-related galactosylation of the N-linked oligosaccharides of human serum IgG. *J Exp Med* 1988;167:1731-6.
3. Ercan A, Barnes MG, Hazen M, Tory H, Henderson L, Dedeoglu F, et al. Multiple juvenile idiopathic arthritis subtypes demonstrate pro-inflammatory IgG glycosylation. *Arthritis Rheum* 2012;64:3025-33.
4. Pucic M, Muzinic A, Novokmet M, Skledar M, Pivac N, Lauc G, et al. Changes in plasma and IgG N-glycome during childhood and adolescence. *Glycobiology* 2012;22:975-82.
5. Kristic J, Vuckovic F, Menni C, Klaric L, Keser T, Beccheli I, et al. Glycans are a novel biomarker of chronological and biological ages. *J Gerontol A Biol Sci Med Sci* 2014;69:779-89.
6. de Haan N, Reidling KR, Driessen G, van der Burg M, Wuhrer M. Changes in healthy human IgG Fc-glycosylation after birth and during early childhood. *J Proteome Res* 2016;15:1853-61.
7. Ercan A, Kohrt WM, Cui J, Deane KD, Pezer M, Yu EW, et al. Estrogens regulate glycosylation of IgG in women and men. *JCI Insight* 2017;2:e89703.
8. Kaneko Y, Nimmerjahn F, Ravetch JV. Anti-inflammatory activity of immunoglobulin G resulting from Fc sialylation. *Science* 2006;313:670-3.
9. Ackerman ME, Crispin M, Yu X, Baruah K, Boesch AW, Harvey DJ, et al. Natural variation in Fc glycosylation of HIV-specific antibodies impacts antiviral activity. *J Clin Invest* 2013;123:2183-92.

Available online October 24, 2019.
<https://doi.org/10.1016/j.jaci.2019.10.012>

Persistent cow's milk allergy is associated with decreased childhood growth: A longitudinal study



To the Editor:

Food allergy is a prevalent problem, with well-described risks involving safety, comorbidities, and quality of life. An expanding body of research suggests that food allergy and elimination diets can also affect childhood growth and nutrition and that allergy to cow's milk (CM)¹⁻⁴ or multiple foods⁵ impart particular risk. Nearly all studies to date have been cross-sectional, and the few longitudinal investigations of growth in children with food allergy have been limited to the first years of life.^{6,7} Data are lacking on growth patterns for children with ongoing food allergy that persists after the early childhood years, raising questions about the long-term effect on body morphology and adult height. Here we present the first description of growth in a longitudinal cohort of children with persistent food allergy that extends from early childhood to adolescence.

A retrospective chart review of patients from the Johns Hopkins Pediatric Allergy Clinic was completed for children with a diagnosis of either persistent CM or peanut and/or tree nut (PN/TN) allergy (and no known history of CM allergy). *Persistent food allergy* was defined as physician-diagnosed IgE-mediated

TABLE I. Study population

	Children with CM allergy (n = 111)	Children with PN/TN allergy (n = 80)	P value
Male sex, no. (%)	68 (61.3)	41 (51.3)	.17
Female sex, no. (%)	43 (38.7)	39 (48.8)	
Race/ethnicity, no. (%)			.12
White	78 (70.3)	67 (83.8)	
Black	9 (8.0)	7 (8.75)	
Hispanic	2 (1.8)	0 (0)	
Asian	10 (8.9)	3 (3.8)	
Other	12 (10.7)	3 (3.8)	
Allergens avoided, no. (%)			
Peanut only	—	4 (5.0)	
Tree nuts only	—	7 (8.8)	
Peanut and tree nut	—	69 (86.3)	
CM	111 (100)	—	
Clinic visits per patient, mean (SD [range])			
2-4 y	2.24 (1.05 [1-6])	1.65 (0.75 [1-4])	<.01
5-8 y	2.46 (1.00 [1-5])	2.20 (1.00 [1-5])	.10
9-12 y	1.68 (0.96 [1-5])	1.44 (0.67 [1-3])	.14
≥13 y*	0.53 (1.04 [0-5])	0.43 (0.98 [0-5])	.32
Comorbid conditions			
Atopic dermatitis, no. (%)			
Any visit	86 (77.5)	53 (66.3)	.07
2- to 4-year-old visit (any)	69 (62.3)	40 (50.0)	.10
5- to 8-year-old visit (any)	69 (62.3)	40 (50.0)	.10
9- to 12-year-old visit (any)	51 (45.9)	30 (47.5)	.24
Asthma or use of asthma medication			
Any visit	98 (88.2)	54 (67.5)	<.01
2- to 4-year-old visit (any)	75 (67.6)	29 (36.3)	<.01
5 to 8-year-old visit (any)	95 (85.6)	46 (57.5)	<.01
9- to 12-year-old visit (any)	90 (81.1)	44 (55.0)	<.01
Rhinitis			
Any visit	96 (86.5)	73 (91.3)	.49
2- to 4-year-old visit (any)	52 (46.8)	45 (56.3)	.24
5- to 8-year-old visit (any)	83 (74.5)	61 (76.3)	>.99
9- to 12-year-old visit (any)	84 (75.7)	61 (76.3)	>.99
Eosinophilic esophagitis/gastrointestinal disease			
Any visit	15 (13.5)	—	
2- to 4-year-old visit (any)	7 (6.3)	—	
5- to 8-year-old visit (any)	6 (5.4)	—	
9- to 12-year-old visit (any)	9 (8.1)	—	
Medication use			
ICS (daily/intermittent)			
Any visit	79 (71.2)	34 (42.5)	<.01
2-4 y	45 (40.5)	19 (23.8)	.02
5-8 y	65 (58.6)	28 (35.0)	<.01
9-12 y	64 (57.7)	26 (32.5)	<.01
Topical corticosteroid (daily/intermittent)			
Any visit	61 (55.0)	38 (47.5)	.38
2-4 y	47 (4.3)	24 (30.0)	.10
5-8 y	35 (31.5)	22 (27.5)	.63
9-12 y	31 (27.9)	16 (20.0)	.24
ICS (daily/intermittent)			
Any visit	52 (46.8)	28 (35.0)	.11
2-4 y	9 (8.1)	10 (12.5)	.34
5-8 y	38 (34.2)	19 (23.8)	.15
9-12 y	34 (30.6)	19 (23.8)	.33
Serum IgE level > predictive threshold†	100 (90.1)	78 (97.5)	.08
History of reaction to food	109 (98.2)	69 (86.3)	<.01
Positive oral food challenge result to food	14 (12.6)	8 (10.0)	.65

Any visit was defined as visits at age 2 to 12 years not including additional data collected after age 13 years. P values were determined by using the Fisher exact test.

*Visits at an age of 13 or more years were not required for study inclusion, but data were collected if available: 21 (26%) of 80 children with PN/TN allergy and 32 (29%) of 112 with CM allergy had at least 1 visit after age 13 years.

†Predictive IgE levels were defined as follows: CM, >15 kU_A/L; peanut, >14 kU_A/L; and tree nut, >0.1 kU_A/L.

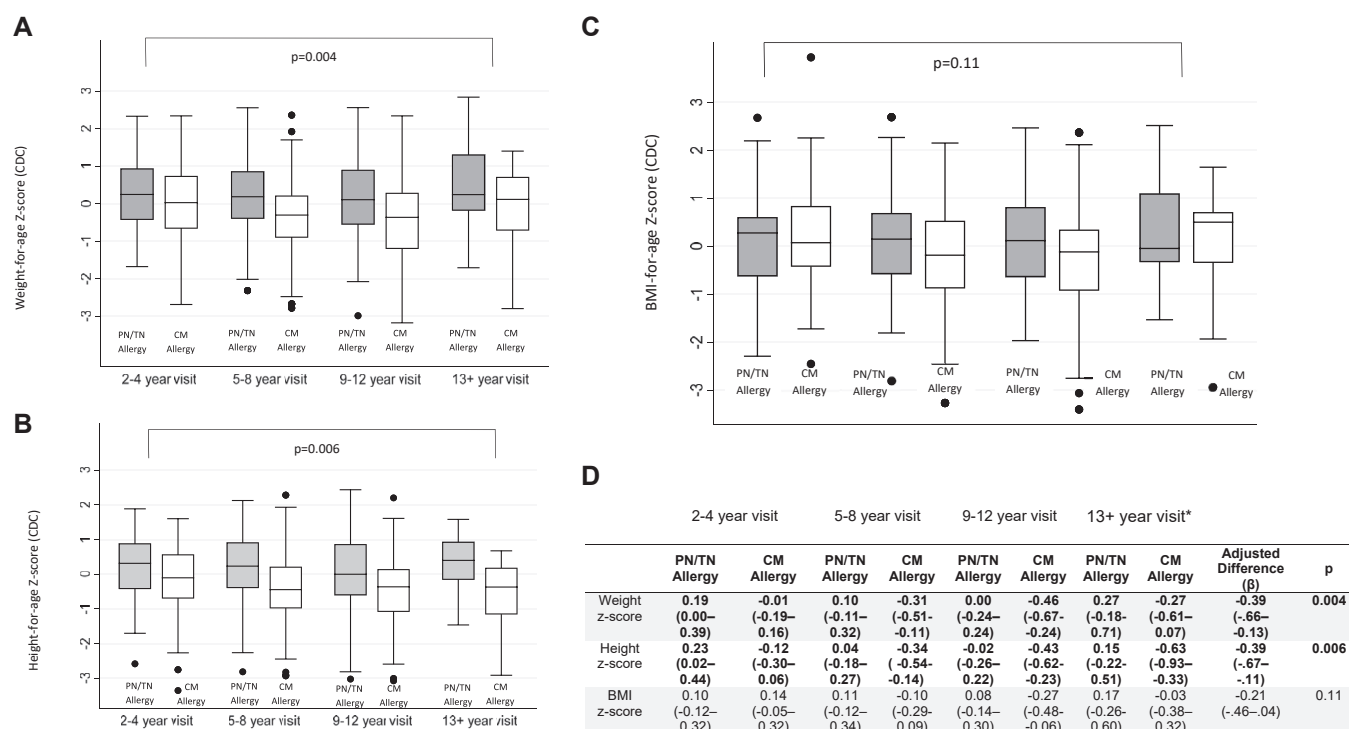


FIG 1. Mean weight (A), height (B), and BMI (C) z scores for children with persistent CM and PN/TN allergy and mean z score differences by age in children with CM allergy and children with PN/TN allergy (D). Box plots of weight, height, and BMI measurements for children with PN/TN allergy and children with CM allergy by age category are shown. Regression analysis with generalized estimating equations was used to account for clustering within subjects, adjusting for age category, sex, and ethnicity. Values are presented with 95% CIs. *Data were collected if available but were not required for inclusion (n = 53; 32 with CM allergy and 21 with PN/TN allergy). CDC, Centers for Disease Control and Prevention.

allergy at age 9 years or older based on a convincing history of clinical symptoms, food-specific IgE levels, skin prick test responses, and/or positive food challenge results. For inclusion, all children were required to have at least 1 clinic visit with complete clinical data (including height and weight measurement) during the following age ranges: 2 to 4, 5 to 8, and 9 to 12 years. Children were also required to adhere to a strict elimination diet (for CM, no extensively heated milk or ingredients were allowed). Children were excluded if they had any other major medical disorder with expected effect on growth.

Clinical data (including comorbid diagnoses, other allergy, and medication use) and anthropometric measurements were recorded for all documented visits between the ages of 2 and 12 years, and additional data were collected, if available, for visits after age 13 years. Differences in mean weight, height, and body mass index (BMI) z scores were determined by using a generalized estimation equation regression model (to adjust for clustering on individual given variation in number of clinic visits), adjusting for age category, sex, and ethnicity. Additional description of the methods used in this study is included in the Methods section in this article's Online Repository at www.jacionline.org. The study was approved by the Johns Hopkins Hospital Institutional Review Board.

One hundred ninety-one children with persistent IgE-mediated allergy (CM, n = 111; PN/TN, n = 80) seen between November 1994 and March 2015 were included in this study. Patients' characteristics are listed in Table I and in Table E1 in this article's

Online Repository at www.jacionline.org. One hundred seventy-eight children had a clinical history of reactivity (either a positive oral food challenge result [n = 22] or a history of convincing reaction to food). Fifty-three children (32 with CM and 21 with PN/TN allergy) had clinical data after age 13 years that were also included for analysis. A total of 1186 clinic visits were included (1098 between the ages of 2 and 12 years). Consistent with previous data, children with CM allergy tended to restrict other major allergens, such as egg, peanut, and tree nuts, and had high prevalence of asthma.^{8,9} Children with CM allergy had lower weight (mean z score difference, 0.39; 95% CI, 0.13-0.66; *P* = .004) and height (mean z score difference, 0.39; 95% CI, 0.11-0.67; *P* = .006) but not BMI-for-age (*P* = .11) z scores compared with children with PN/TN allergy (Fig 1), adjusting for age, sex, and ethnicity. Findings were unaffected by other atopic conditions (asthma, rhinitis, early-onset or any eczema, and eosinophilic esophagitis) or inhaled corticosteroid (ICS) use.

Persistent CM allergy was also associated with a greater decrease in weight and also BMI z scores from the baseline visit (2-4 years of age) at older ages (weight: mean z score difference, 0.25; 95% CI, 0.06-0.43; *P* = .008; BMI: mean z score difference, 0.34; 95% CI, 0.09-0.59; *P* = .007; see Table E2 in this article's Online Repository at www.jacionline.org). These differences were larger in the 5- to 8-year-old (mean z score difference, 0.43; 95% CI, 0.13-0.73; *P* = .004) and 9- to 12-year-old (mean z score difference, 0.52; 95% CI, 0.21-0.84; *P* = .001) age ranges than in the less than 5-year-old age range for weight but not height

($P < .05$ for interaction with age; see Table E3 in this article's Online Repository at www.jacionline.org). However, there was a trend toward greater height differences at the older ages also (mean z score differences, 0.38 [95% CI, 0.07-0.69; $P = .02$] at age 5-8 years and 0.42 [95% CI, 0.11-0.74; $P = .01$] at age 9-12 years; P value for interaction with age $> .25$). There were no increased odds for very low height or weight measures (z score < -2) detected in children with milk allergy that would correspond to stunting or wasting (data not shown). For the children with clinical data at age 13 years or older ($n = 53$), adjusted differences in weight and height were more pronounced for children with milk allergy (weight: mean z score difference, -0.63 ; 95% CI, 0.09-1.17; $P = .02$; height: mean z score difference, -0.82 ; 95% CI, 0.36-1.28; $P \leq .01$; Fig 1), and there remained no significant differences in BMI. ICS exposure alone was not a predictor of growth differences.

It is unclear whether these findings predict final adult height and body measures, but our data raise important questions regarding the potential effect of persistent food allergy on growth and development. Both early childhood and puberty are periods punctuated by increased growth requirements in the normal state. If these patterns are significantly influenced by allergic status and diet, there could be long-term effects that are not well described to date. Our findings are consistent with a recent report from Sinai et al⁴ that demonstrates growth deficiencies in a cross-sectional study of postpubertal patients with CM allergy, suggesting that young adults with CM allergy might not reach their growth potential. It is also important to note that the phenotype of CM allergy appears to often be one of multiple food allergies.

There are some notable limitations to our study, including recruitment from a single referral center and requirement for long-term follow-up, introducing a potential selection bias for patients with greater morbidity. We lacked a true control population; however, this was addressed by comparison of children with CM allergy with those who avoided only PN/TN (which might be expected to have a lesser overall effect on the diet). However, selection of this control group might result in underestimation of the relationship between CM allergy and childhood growth. Management of CM allergy has evolved in recent years, and it is possible that some subjects who avoided milk strictly in this study would now be offered baked milk challenges (which were used more routinely starting in the late 2000s). Also, during the time period included here, we saw improved access and referral for dietetic advice, improved availability of allergen-free foods and nutritional alternatives, and passage of the FALCPA law (2004) to allow for more clear identification of food allergen ingredients. As such, the effect of food allergy on growth might now be different. We noted growth differences, yet patients' measurements did not deviate to a large extent from the normal range. Diagnoses were not all challenge confirmed; however, nearly all patients reported a history of clinical reactivity, and all avoided CM.

Because of the retrospective nature of the study, we could not assess nutritional supplementation or guidance, adequacy of diet, eczema or asthma severity, or cumulative corticosteroid use. Still, our findings are reflective of the phenotype of persistent CM allergy, which is likely influenced by a number of factors that might contribute to a picture of disease that is not entirely explained by simple nutritional inadequacy.

In conclusion, we found that in a longitudinal cohort of children with persistent IgE-mediated food allergy, those with

CM allergy were smaller and lighter than peers with limited PN/TN allergy, and these differences persisted to early adolescence and beyond. Weight differences increased with advancing age, and there was a trend toward greater differences in height also at older ages. For those children who had ongoing allergy and clinical data available into the teenage years, weight and height differences persisted and appeared more pronounced. To our knowledge, this is the first study to characterize growth trajectory in children with persistent food allergy and only longitudinal analysis to date to follow growth through childhood.

Karen A. Robbins, MD^a

Robert A. Wood, MD^b

Corinne A. Keet, MD, PhD^b

From ^athe Division of Allergy and Immunology, Children's National Health System, Washington, DC, and ^bthe Division of Pediatric Allergy and Immunology, Johns Hopkins University School of Medicine, Baltimore, Md. E-mail: karenrobbinsmd@gmail.com.

Disclosure of potential conflict of interest: The authors declare that they have no relevant conflicts of interest.

REFERENCES

- Hobbs CB, Skinner AC, Burks AW, Vickery BP. Food allergies affect growth in children. *J Allergy Clin Immunol Pract* 2015;3:133-4.
- Jhamnani RD, Levin S, Rasooly M, Stone KD, Milner JD, Nelson C, et al. Impact of food allergy on the growth of children with moderate-severe atopic dermatitis. *J Allergy Clin Immunol* 2018;141:1526-9.
- Robbins KA, Wood RA, Keet CA. Milk allergy is associated with decreased growth in US children. *J Allergy Clin Immunol* 2014;134:1466-8.
- Sinai T, Goldberg MR, Nachshon L, Amitzur-Levy R, Yichie RD, Katz Y, et al. Reduced final height and inadequate nutritional intake in cow's milk-allergic young adults. *J Allergy Clin Immunol Pract* 2019;7:509-15.
- Flammarion S, Santos C, Guimber D, Jouannic L, Thumerelle C, Gottrand F, et al. Diet and nutritional status of children with food allergies. *Pediatr Allergy Immunol* 2011;22:161-5.
- Beck C, Koplin J, Dharmage S, Wake M, Gurrin L, McWilliam V, et al. Persistent food allergy and food allergy coexistent with eczema is associated with reduced growth in the first 4 years of life. *J Allergy Clin Immunol Pract* 2016;4:248-56.
- Tuokkola J, Luukkainen P, Nevalainen J, Ahonen J, Toppari J, Ilonen J, et al. Eliminating cow's milk, but not wheat, barley, or rye, increases the risk of growth deceleration and nutritional inadequacies. *Acta Paediatrica* 2017;106:1142-9.
- Skripak JM, Matsui EC, Mudd K, Wood RA. The natural history of IgE-mediated cow's milk allergy. *J Allergy Clin Immunol* 2007;120:1172-7.
- Wood RA, Sicherer SH, Vickery BP, Jones SM, Liu AH, Fleischer DM, et al. The natural history of milk allergy in an observational cohort. *J Allergy Clin Immunol* 2013;131:805-12.

Available online November 6, 2019.
<https://doi.org/10.1016/j.jaci.2019.10.028>

Characterization of longitudinal wheeze phenotypes from infancy to adolescence in Project Viva, a prebirth cohort study



To the Editor:

Longitudinal trajectories of symptom data, particularly for episodic outcomes, are especially useful for capturing dynamic phenotypes that vary by stage of life. Wheeze is a prevalent airway symptom in infancy and early childhood that might be transitory in nature and is known to be an important predictor of later wheeze and development of asthma.¹ Although longitudinal wheeze trajectories overlap with asthma case status, patterns of symptom heterogeneity over time might further delineate the dynamics of disease progression, remittance of asthma, or both and

METHODS

Study design/population

A retrospective chart review of clinic records for patients seen in the Pediatric Allergy Clinic at Johns Hopkins between 1994 and 2015 was completed, selecting for children who had diagnosis of either persistent IgE-mediated CM allergy or PN/TN allergy (with no known history of milk allergy) at age 9 years or older. All children were required to have at least 1 clinic visit for food allergy with complete clinical documentation, including height and weight measurement, during the following age ranges: 2 to 4 years, 5 to 8 years, and 9 to 12 years. Additional visits during these age ranges were also included, if available.

Data were included if the child adhered to a strict allergen avoidance diet but not subsequent to passed challenge or challenges and/or introductions of any form of CM (including extensively heated milk) or PN/TN for the 2 respective groups. In the group with PN/TN allergy, we only allowed for concurrent food allergy or avoidance of nonsoy legumes and sesame allergy because allergies to these are frequently associated with allergy to nuts but are unlikely to have significant independent nutritional consequence. In the group of children with allergy to CM, we allowed for the presence of food allergy to any other foods, including peanut and tree nuts, given the frequent co-occurrence of multiple food hypersensitivities with the milk allergy phenotype and relative rarity of isolated milk allergy. Other food avoidances were noted at every visit and summarized by age range in [Table E1](#). Data were collected for each visit if there were multiple clinic visits during the aforementioned age ranges and also if patients had additional visits at or after age 13 years. Clinic visits with missing height and/or weight measurements were not included in the analysis. Race/ethnicity was defined by entry in the electronic medical record at patient registration.

Data on medication use were collected, including use of topical corticosteroids, intranasal corticosteroids, ICSs, and other asthma medications. However, given the extended intervals between visits and the tendency of

patients to use these medications with variable consistency, we were unable to quantify exposure to these medications with precision. Therefore corticosteroid exposure was defined as any use of these medications (daily or intermittent) noted at a clinic visit.

Statistical analysis

Age-adjusted z scores for height, weight, and BMI for age and sex were calculated by using the Centers for Disease Control and Prevention's Epi Info software package (Epi Info v.3.5.4; July 23, 2008), with comparison with Centers for Disease Control and Prevention reference growth curves (2000). Analysis was completed with STATA SE/12.1 software (StataCorp, College Station, Tex). Extreme outliers, defined as ± 5 or more z scores, were excluded, and sensitivity analysis also was then completed for outliers of 2 or more z scores to ensure plausibility of measurements. Between-group comparisons for baseline characteristics and clinical features used the Fisher exact test for categorical measures presented with means, SDs, and ranges. P values of less than .05 were considered statistically significant. Differences in mean weight, height, and BMI z scores were determined by using a generalized estimating equation regression model (to adjust for clustering on individual given variation in number of clinic visits per individual in each age range), adjusting for age category, sex, and ethnicity. Changes from baseline z scores were calculated as differences in mean weight, height, and BMI-for-age z scores compared with the initial visit (2-4 years of age).

An interaction term was added to evaluate whether differences in anthropometric measures observed between groups were modified by age, ICS use, or both. For the latter variable, ICS exposure was defined as exposure at (1) early age (2-4 years), (2) any visit, or (3) all visit categories. Logistic regression with generalized estimating equation models were used to explore odds for very low growth measures ($< -2 z$).

TABLE E1. Study population

	CM allergy (n = 111)			PN/TN allergy* (n = 80)		
	2-4 y	5-8 y	9-12 y	2-4 y	5-8 y	9-12 y
Other foods avoided, no. (%)†						
Egg	96 (86.5)	97 (87.4)	83 (74.8)	—	—	—
Wheat	50 (45.0)	39 (35.1)	28 (25.2)	—	—	—
Soy	45 (40.5)	23 (20.7)	22 (19.8)	—	—	—
Fish	65 (58.6)	42 (37.8)	29 (26.1)	—	—	—
Shellfish	72 (64.9)	66 (59.5)	46 (41.4)	—	—	—
Sesame	35 (31.5)	48 (43.2)	45 (40.5)	8 (10.0)	9 (11.3)	10 (12.5)
Non-soy legume(s)	20 (18.0)	25 (22.5)	26 (23.4)	1 (1.3)	3 (3.8)	1 (1.3)
Peanut	105 (94.6)	97 (87.4)	86 (77.5)	NA	NA	NA
Tree nuts	98 (88.3)	96 (86.5)	93 (83.8)	NA	NA	NA

Visits at 13 or more years of age were not required for study inclusion, but data were collected if available: 21 (26%) of 80 children with PN/TN allergy and 32 (29%) of 112 children with CM allergy had at least 1 visit at age 13 years or older.

NA, Not available.

*Other food avoidance was limited to sesame and non-soy legumes.

†Food avoidance noted at any visit during the age range is shown. Children might have not incorporated other foods (eg, egg or wheat) for nonallergic reasons, but these data were not able to be collected.

TABLE E2. Mean change from baseline (2 to 4 years old) z scores for weight, height, and BMI in children with CM versus PN/TN allergy

Δ z Score from baseline visit	CM allergy (n = 112)			PN/TN allergy (n = 80)			Adjusted difference (β)	P value
	2-4 y	5-8 y	9-12 y	2-4 y	5-8 y	9-12 y		
Weight for age	—	-0.30 (-0.43 to -0.16)	-0.44 (-0.60 to -0.28)	—	-0.06 (-0.21 to 0.09)	-0.16 (-0.35 to 0.04)	-0.25 (-0.43 to -0.06)	<.01
Height for age	—	-0.19 (-0.34 to -0.04)	-0.28 (-0.43 to -0.13)	—	-0.18 (-0.29 to -0.06)	-0.24 (-0.39 to -0.08)	-0.04 (-0.20 to 0.13)	.7
BMI for age	—	-0.24 (-0.39 to -0.09)	-0.41 (-0.60 to -0.22)	—	0.05 (-0.17 to 0.27)	0.03 (-0.23 to 0.29)	-0.34 (-0.59 to -0.09)	<.01

Mean differences were determined by using multivariate linear regression (general estimating equation for clustering within subjects), adjusting for age category, sex, and ethnicity. Values are presented with 95% CIs. Values in boldface indicate statistical significance.

TABLE E3. Interaction of age on weight-for-age, height-for-age, and BMI-for-age z score differences in children with CM versus PN/TN allergy

		5-8 years old		9-12 years old		≥13 years old*	
2-4 years old		β	P value	β	P value	β	P value
Weight-for-age	Baseline	-0.24 (-0.42 to -0.05)	.01	-0.28 (-0.53 to -0.02)	.03	-0.07 (-0.52 to 0.37)	.75
Height-for-age	Baseline	-0.05 (-0.20 to 0.10)	.50	-0.10 (-0.29 to 0.10)	.32	-0.20 (-0.53 to 0.14)	.25
BMI-for-age	Baseline	-0.32 (-0.59 to -0.06)	.02	-0.42 (-0.76 to -0.08)	.02	-0.17 (-0.68 to 0.33)	.50

Mean differences were determined by using multivariate linear regression (general estimating equation for clustering within subjects), adjusting for age category, sex, and ethnicity, are shown. Values are presented with 95% CIs. Values in boldface indicate statistical significance.

*Data were collected if available but not required for inclusion (n = 53; 32 with CM allergy and 21 with PN/TN allergy).