

Children with East Asian-Born Parents Have an Increased Risk of Allergy but May Not Have More Asthma in Early Childhood



Noor H.A. Suaini, BSc (Hons)^{a,b}, Jennifer J. Koplin, PhD^{b,c}, Rachel L. Peters, PhD^{a,b}, Mari Sasaki, MD^b, Justine A. Ellis, PhD^{a,d,e}, David J. Martino, PhD^{a,b,f}, Adrian J. Lowe, PhD^{b,c}, Mimi L.K. Tang, MBBS, FRACP, FRCPA, PhD^{a,b,g}, Anne-Louise Ponsonby, BMedSci, MBBS, PhD^{b,c}, Lyle C. Gurrin, PhD^c, Shyamali C. Dharmage, MBBS, MSc, MD, PhD^c, and Katrina J. Allen, MBBS, FRACP, PhD, FAHMS^{a,b,g,h}; for the HealthNuts study group *Parkville, Carlton, and Burwood, Victoria, Australia; and Manchester, United Kingdom*

What is already known about this topic? Infants with East Asian-born parents living in Melbourne have a higher risk of IgE-mediated food allergy than those with Caucasian-born parents. It is unclear if this increased risk extends to other allergic diseases later in childhood.

What does this article add to our knowledge? IgE-mediated food allergy and eczema at age 1 increase the risk of asthma and allergic rhinitis at age 6, but this association was not modified by ancestry. Children with East Asian-born parents do go on to have more allergic diseases at age 6 years, whereas atopic asthma appears to be similar to children with Caucasian-born parents.

How does this study impact current management guidelines? Clinicians will be able to use these data to better inform parents of East Asian children on the progression of their child's allergic diseases early in their childhood. Future prevention and management approaches to allergic diseases can be tailor-made and targeted to this population.

BACKGROUND: We previously reported that infants with Asian-born parents are 3 times more likely to have IgE-mediated food allergy than those with Australian-born parents. It is unknown whether this translates to the increased risk of other allergic diseases later in childhood and whether ancestry interacts with other risk factors for allergic disease development.

OBJECTIVE: To compare prevalence and risk factors for allergic rhinitis, asthma, and aeroallergen sensitization at age 6 between children with East Asian-born and Caucasian-born parents.

METHODS: A total of 5276 1-year-old infants were recruited into a population-based longitudinal study of allergy. A total of

4455 children participated in age 6 follow-up (84.4%), including 3015 with Caucasian-born parents and 415 with East Asian-born parents. Children underwent skin prick tests to aeroallergens and questionnaires captured data on asthma, eczema, and allergic rhinitis.

RESULTS: Compared with children with Caucasian-born parents, children of East Asian-born parents had more allergic rhinitis (19.9% [95% confidence interval (CI) 14.9-26] vs 9.3% [95% CI 8-10.8], $P < .001$) and aeroallergen sensitization (64.3% [95% CI 57.5-70.5] vs 34.4% [95% CI 32.2-36.7], $P < .001$) at age 6. Asthma was similar in both groups (9.1%

^aDepartment of Paediatrics, University of Melbourne, Parkville, Victoria, Australia

^bCentre for Food and Allergy Research, Murdoch Children's Research Institute, Parkville, Victoria, Australia

^cThe School of Population and Global Health, University of Melbourne, Carlton, Victoria, Australia

^dCentre for Social and Early Emotional Development, Faculty of Health, Deakin University, Burwood, Victoria, Australia

^eGenes, Environment & Complex Disease, Murdoch Children's Research Institute, Parkville, Victoria, Australia

^fTelethon Kids Institute, University of Western Australia, Perth, Western Australia, Australia

^gDepartment of Allergy and Clinical Immunology, Royal Children's Hospital, Parkville, Victoria, Australia

^hInstitute of Inflammation and Repair, University of Manchester, Manchester, United Kingdom

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Conflicts of interest: M. L. K. Tang is on the Nestle Nutrition Institute Medical Advisory Board Oceania; is a past member of the Danone Nutricia Global Scientific Advisory Board; has received consultancy fees from Deerfield Consulting, GLG Consulting, and Bayer; is employed by and has stock/stock options in ProTA Therapeutics; has received lecture fees from Danone Nutricia and Nestle Health Sciences; has a patent owned by Murdoch Children's Research Institute; received royalties from Wilkinson Publishing; and has received payment for developing educational presentations from MD Linx. K. J. Allen serves as a consultant for Nestle, ThermoFisher, AspenCare, Before Brands, and Nutricia. The rest of the authors declare that they have no relevant conflicts of interest.

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Corresponding author: Katrina J. Allen, MBBS, FRACP, PhD, FAHMS, Murdoch Children's Research Institute, Royal Children's Hospital, Flemington Road, Parkville 3052, Victoria, Australia. E-mail: katrina.allen@mcri.edu.au.

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Abbreviations used

CI- Confidence interval

ISAAC- International Study of Asthma and Allergies in Childhood

OFC- Oral food challenge

PR- Prevalence ratio

SACC- Standard Australian Classification of Countries

SPT- Skin prick test

[95% CI 6.2-13.2] vs 11.7% [95% CI 10.4-13.1]), $P = .21$. **Children with IgE-mediated food allergy and eczema in infancy were 3 times more likely to have asthma and 2 times more likely to have allergic rhinitis at age 6, irrespective of ancestry.**

CONCLUSIONS: Children of East Asian ancestry born in Australia have a higher burden of most allergic diseases in the first 6 years of life, whereas asthma may follow a different pattern. IgE-mediated food allergy and eczema at age 1 increase the risk of asthma and allergic rhinitis irrespective of ancestry. © 2018 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2019;7:539-47)

Key words: Allergic rhinitis; Ancestry; Asians; Asthma; Children; Eczema; Ethnicity; Food allergy; Hay fever

There is increasing evidence that the risk of allergic disease differs according to both ancestry and the environment in early life. We previously showed that children of Asian descent who were born in Australia had very high rates of eczema and food allergy in early life,^{1,2} with up to 50% of infants with both parents born in East Asia having eczema and 25% having challenge-confirmed food allergy by 1 year of age.³ In contrast, children who were born in Asia and subsequently migrated to Australia in early childhood appeared to be protected from developing food allergy.¹ This difference in allergy prevalence by both ancestry and country of birth is not limited to Australia. A study in the United States found that children born outside the United States had a lower risk of food sensitization than those born in the United States, whereas the highest risk of food sensitization was seen among children born in the United States to migrant parents.⁴ Another study in the United Kingdom found an over-representation of non-Caucasian children in a pediatric allergy clinic.⁵

Despite the amplified burden of allergic disease in infancy among children of Asian ancestry who are born in Australia, little is known about their risk of allergic disease later in life. In general, it has been estimated that of those with eczema during the first 4 years of life, around one-third progress to develop asthma and two-thirds develop allergic rhinitis.⁶⁻⁸ It is also generally accepted that early life food allergy and eczema clinically coassociate.⁹ Less is known about the role of food allergy in the development of the atopic march to asthma and allergic rhinitis, although we have previously reported that children with food allergy at age 1 year were more likely to have a doctor diagnosis of asthma at 4 years of age and that the risk was highest for children with food allergy and coexistent eczema in infancy.¹⁰ It is not known whether the atopic march is modified by ancestry or country of birth.

As such, the aims of this study were: (1) to compare the prevalence of allergic rhinitis, asthma, and aeroallergen sensitization in Australian children with East Asian-born and

Caucasian-born parents at age 6 years and (2) to investigate whether the associations between IgE-mediated food allergy and eczema in the first year of life and allergic disease at age 6 years differ depending on ancestry, using data from our recently completed age 6 follow-up of the HealthNuts population-based longitudinal study of allergic disease.

METHODS**Study population**

The HealthNuts study is a longitudinal population-based cohort study of allergic disease in Melbourne, Australia. The recruitment process has previously been described in detail.¹¹ Briefly, 5276 twelve-month-old infants were recruited from immunization clinics around Melbourne (74% participation rate). All infants underwent a skin prick test (SPT) at recruitment to 4 foods (egg, peanut, sesame, shrimp/cow's milk) (ALK-Abello, Madrid, Spain). Infants with a detectable wheal size ≥ 1 mm to any of the foods were invited to the HealthNuts clinic at the Royal Children's Hospital, Melbourne, for an oral food challenge (OFC) to ascertain their food allergy status. OFCs were carried out using a predetermined protocol as previously described.^{11,12}

Age 6-year follow-up. At 6 years of age, all children ($N = 5276$) were invited to attend a HealthNuts allergy clinic at the Royal Children's Hospital. Home visit assessments were offered for those who were unable to attend the hospital. Parents completed a questionnaire that included general information about the child as well as family and the child's history of asthma, wheeze, allergic rhinitis, and eczema. We also incorporated questions on asthma, eczema, and allergic rhinitis from the validated International Study of Asthma and Allergies in Childhood (ISAAC).¹³ Those who did not complete the full questionnaire were given the option to complete a short telephone questionnaire, which asked a limited number of questions including whether the child had ever been diagnosed with asthma or allergic rhinitis.

Skin prick tests. At age 6 years, all children who participated in an assessment, either at the Royal Children's Hospital or home visit, underwent a SPT to peanut, egg, sesame, soy, almond, cashew, hazelnut, shellfish, cow's milk, wheat, house dust mite, rye grass, Bermuda grass, cat hair, alternaria, birch mix, cladosporium, and dog hair. Aeroallergen sensitizations were determined in the whole cohort only at age 6. SPTs were carried out with a single-tine lancet (Stallergenes, Antony, France) on the child's back using allergen extracts (ALK-Abello) including a positive control (10 mg/mL histamine) and a negative control (saline). Wheal size was measured after 15 minutes and calculated as the average of the longest diameter and the diameter perpendicular to it and then subtracting the negative control SPT diameter.

Definitions

Ancestry. Parental country of birth was used as a proxy for ancestry background. We have shown previously that parental country of birth information correlated well with genetically inferred ancestry (93.7% correlation for "Caucasians" and 93.0% correlation for "Asians").¹⁴ For this analysis, we focused on 2 groups, East Asians and Caucasians. Caucasians refer to children with both parents being born in Australia, the United Kingdom, or Europe. The East Asian group was made up of children with 1 or 2 East Asian-born parents, as defined in one of our previous studies.³ Our East Asian definition included countries in the North East Asia region such as China,

Hong Kong, Japan, Taiwan, Macau, North Korea, South Korea, and South East Asia region of Vietnam, Philippines, Singapore, Thailand, Indonesia, Malaysia, Cambodia, and Laos. Groupings were based on the Standard Australian Classification of Countries (SACC) that were developed to be relevant to Australia's multicultural society for use in analyzing Australian-based country of origin data.¹⁵ Groups in the SACC comprise geographically proximate countries that have broadly similar social, cultural, economic, and political characteristics. All other country groups (eg, South Asians, Middle East, and Africa) were not included in the analyses due to small numbers. We also correlated parental country of birth with self-reported grandparents' ancestry. Eighty-seven percent of children classified in the East Asian group had at least 1 set of grandparents reporting Asian as their ancestry, whereas 80% of those in the Caucasian group had both sets of grandparents reporting as Caucasian.

Definitions for allergy at age 1 year

Food allergy. Food allergy is defined as a positive OFC outcome or recent reaction consistent with our OFC stopping criteria¹² to peanut, sesame, or egg, in conjunction with a positive sensitization test (SPT with wheal size ≥ 2 mm greater than negative control and/or sIgE > 0.35 kU/L). A positive OFC was defined as more than 3 noncontact urticarial reactions lasting more than 5 minutes, angioedema, vomiting, or anaphylaxis, within 2 hours of the last challenge dose. On discharge, those with a negative challenge (able to tolerate top dose of challenged food without any subsequent allergic reactions) were administered a single serving of the challenged food at home for 7 days to capture any late reactions.

Infantile eczema. Infantile eczema is defined as parent report doctor diagnosis of eczema during the first year of life.

Definitions for allergy at age 6

Eczema. Parent report of an itchy rash in the last 12 months that affected typical eczema locations, such as folds of elbows and knees.¹⁶

Aeroallergen sensitization. Positive SPT wheal ≥ 3 mm greater than negative control for any of the following aeroallergens: house dust mite, rye grass, Bermuda grass, cat hair, alternaria, birch mix, cladosporium, and dog hair.

Allergic rhinitis. Allergic rhinitis was defined as nose symptoms in the last 12 months accompanied by itchy watery eyes^{13,16} in the presence of aeroallergen sensitization.

Asthma. Asthma was defined as parent report of a doctor diagnosis of asthma and either wheeze or use of asthma medication in the last 12 months.

Atopic asthma. We also further classified asthma into atopic asthma (asthma with aeroallergen sensitization) and nonatopic asthma (asthma with no aeroallergen sensitization).^{17,18}

Statistical analysis

This is a *post hoc* cohort analysis, as a follow-up to our previous study that found children with East Asian-born parents have an increased risk of food allergy at age 1 year.³

Prevalence estimates. The prevalence of allergy outcomes at age 6 years in each ancestry group was estimated as the observed proportion with 95% confidence intervals (CIs) generated using the normal approximation to the binomial distribution. To control for

the potential impact of differential loss to follow-up, we adjusted for differences in demographic characteristics and other potential risk factors between participants who completed the full questionnaire at age 6 years and those who were lost to follow-up/not included in the analysis, using the inverse probability weighting method described by Little and Rubin¹⁹ (see [Online Repository](http://www.jaci-inpractice.org) at www.jaci-inpractice.org for details).

Regression models. For each ancestry, the association between allergy status at age 1 (food allergy and infantile eczema) and risk of asthma and allergic rhinitis at age 6 was estimated using binomial regressions (a generalized linear model with a logarithm link function) to obtain estimates of prevalence ratios (PRs) and 95% CIs for the corresponding population parameter. Interaction analyses between ancestry and food allergy and eczema at age 1 year were tested by adding product terms to the regression model.

Wheezing in the first year of life could be an early indicator of asthma.²⁰ Therefore, to investigate the longitudinal association between food allergy at age 1 year and the subsequent development of asthma, that is, to assess newly incident disease after age 1, we repeated our analyses after excluding children with wheezing in the first year of life.

The regression analyses were adjusted for the following potential confounders based on previous published literature: sex, socioeconomic status, and parent's or sibling's history of asthma, eczema, allergic rhinitis, or food allergy. Additional potential confounders considered include the presence of cat or dog in the household, household smoking, maternal smoking during pregnancy, mode of delivery, antibiotic use in the first year of life, birthweight (<2500 g vs ≥ 2500 g), duration of breastfeeding, number of siblings, and season of birth (winter vs other).^{21,22} These were included in the regression models if they changed the magnitude of the association between the exposure and outcome by more than 10% on the PR scale.

Sensitivity analyses. We performed the following sensitivity analyses for our regression models, to examine the potential impact of loss to follow-up on our results, and to examine whether our findings were robust to different definitions of asthma and allergic rhinitis:

- (1) To control for the potential impact of differential loss to follow-up, we adjusted for differences in demographic characteristics and other potential risk factors between participants who completed the full questionnaire at age 6 years and those who were lost to follow-up/not included in the analysis, using the inverse probability weighting method described by Little and Rubin¹⁹ (see [Online Repository](http://www.jaci-inpractice.org) at www.jaci-inpractice.org for details).
- (2) To reduce the amount of missing data at age 6 years, we combined data on asthma and allergic rhinitis diagnosis from the full and short questionnaire, and repeated the analysis to examine consistency of our results while using data from a greater percentage of the original cohort.
- (3) To examine whether our findings were robust when using different definitions of asthma and allergic rhinitis, we repeated the analyses using the ISAAC definitions of asthma (answering Yes to both questions "Has your child ever had wheezing or whistling in the chest at any time in the past?" and "Has your child had wheezing in the past 12 months?") and allergic rhinitis (answering Yes to both questions "Has your child ever had sneezing or runny or blocked nose when he/she did not have a

TABLE I. Demographics and baseline characteristics of study population included in main analyses that included children with full questionnaire only

Characteristic	Caucasian (n = 2620)	East Asian (n = 352)	P value
Demographics			
Birthweight, g (mean, range)	3451 (630-5160)	3208 (692-4690)	.032
Male	1323 (50.7)	204 (58.6)	.005
Infant's season of birth			
Summer	597 (22.8)	77 (21.9)	.319
Autumn	638 (24.4)	75 (21.3)	
Winter	701 (26.8)	93 (26.4)	
Spring	683 (26.1)	107 (30.4)	
Caesarean delivery	863 (33)	110 (31.3)	.53
≤ 36 wk of gestation	144 (5.7)	23 (7)	.354
Quintiles of SEIFA disadvantage			
1 (most disadvantaged)	451 (17.2)	53 (15.1)	.416
2	538 (20.6)	84 (23.9)	
3	577 (22.1)	79 (22.4)	
4	548 (21)	64 (18.2)	
5 (least disadvantaged)	501 (19.2)	72 (20.5)	
Family history of asthma, eczema, allergic rhinitis, or food allergy	1956 (74.7)	244 (69.3)	.032
Environmental exposure			
No. of siblings			
No siblings	1306 (50.3)	189 (54)	.213
1 sibling	864 (33.2)	116 (33.1)	
2 siblings	337 (13)	32 (9.1)	
3 or more siblings	92 (3.5)	13 (3.7)	
Use of antibiotics	1293 (51)	150 (44.5)	.026
Childcare attendance	741 (28.3)	78 (22.2)	.016
Cat ownership	514 (19.6)	21 (6)	<.001
Dog ownership	976 (37.3)	52 (14.8)	<.001
Household smoking	504 (19.3)	65 (18.5)	.703
Maternal smoking during pregnancy	105 (4)	2 (0.6)	.001
Infant's diet			
Any breastfeeding	2498 (95.8)	341 (97.2)	.233
Exclusive breastfeeding	1398 (61.3)	148 (47.9)	<.001
Any formula feeding	1856 (76.3)	285 (84.6)	.001

SEIFA, Socio-Economic Indices for Areas.

cold or flu?" and "In the past 12 months, has your child had a problem with sneezing or a runny or blocked nose when he/she did not have a cold/flu?"¹³

The results of each sensitivity analysis are reported in the [Online Repository](http://www.jaci-inpractice.org) at www.jaci-inpractice.org.

All analyses were performed using Stata 15 for Windows (Stata-Corp LP, College Station, Tex). Venn diagrams were obtained using Venn Diagram Plotter (PNNL, Richland, Wash).²³ The Venn Diagram Plotter is supported by the W.R. Wiley Environmental Molecular Science Laboratory, a national scientific user facility sponsored by the US Department of Energy's Office of Biological and Environmental Research and located at PNNL. PNNL is operated by Battelle Memorial Institute for the US Department of Energy under contract DE-AC05-76RL0 1830.

Ethics approval

Ethics approval was obtained from the Royal Children's Hospital Human Research Ethics Committee (reference nos. 27047 and 32294).

RESULTS

Study population

Of the 5276 infants recruited at 12 months, 84% participated in the age 6 follow-up, with a majority answering the full questionnaire (n = 3663). An additional 605 participants completed the short questionnaires and were included in our sensitivity analyses (see [Figure E1](#), available in this article's [Online Repository](http://www.jaci-inpractice.org) at www.jaci-inpractice.org). Assessments including SPT were completed by 3233 children at age 6 years. Demographic and baseline characteristics of the study population are provided in [Table I](#).

Prevalence of allergic diseases at age 6

Allergic rhinitis and eczema at 6 years of age were more common in East Asian children than Caucasian children ([Figure 1](#)). Allergic rhinitis was present in 19.9% (95% CI 14.9-26.0) of East Asian children and 9.3% (95% CI 8.0-10.8) of Caucasian children ($P < .001$). Eczema was present in 26.0% (95% CI 21.0-31.7) of East Asian children

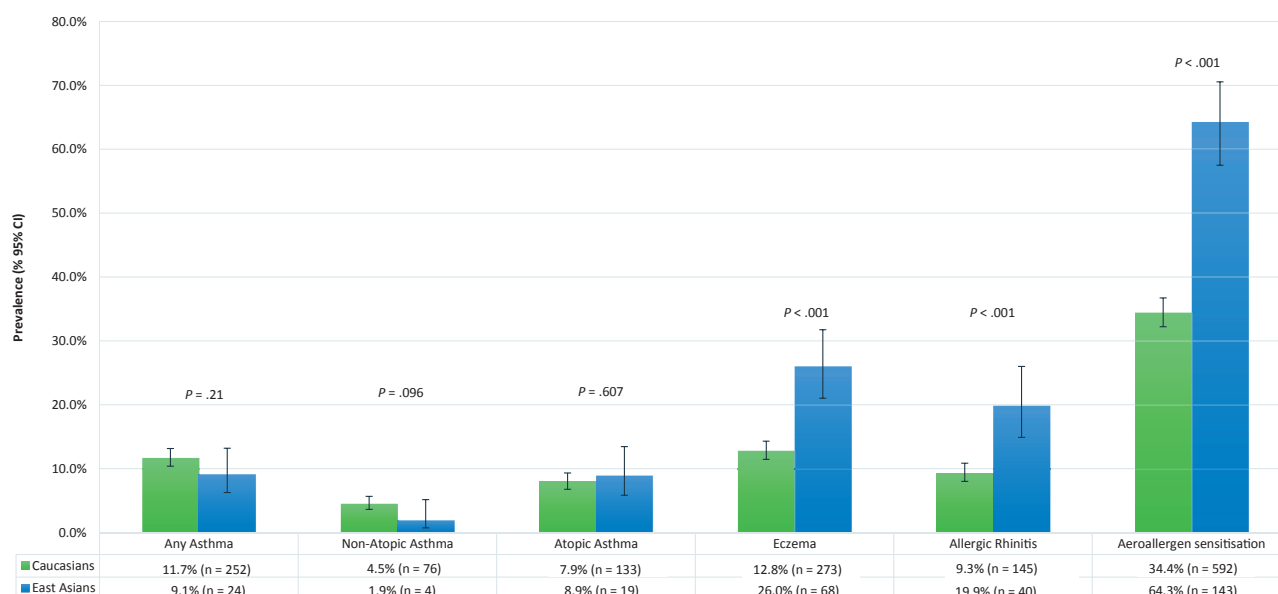


FIGURE 1. Weighted prevalence of asthma, allergic rhinitis, eczema, and atopic asthma at age 6, stratified by ancestry, with 95% confidence interval. Prevalence estimates were adjusted (weighted) for differences in demographic characteristics and other potential risk factors between participants who completed the full questionnaire at age 6 years and those who were lost to follow-up/not included in the analysis, using the inverse probability weighting method described by Little and Rubin¹⁹ (see [Online Repository at www.jaci-inpractice.org](http://www.jaci-inpractice.org) for details).

and 12.8% (95% CI 11.5-14.3) of Caucasian children ($P < .001$).

The prevalence of aeroallergen sensitization was also higher in East Asian children, with 64.3% (95% CI 57.5-70.5) sensitized to at least 1 aeroallergen compared with 34.4% (95% CI 32.2-36.7) of Caucasian children ($P < .001$). When aeroallergens were examined individually, sensitization to each of the tested allergens was higher in the East Asian children (data not shown).

Conversely, asthma prevalence was similar in East Asian and Caucasian children, affecting 9.1% (95% CI 6.2-13.2) of East Asian children and 11.7% (95% CI 10.4-13.1) of Caucasian children ($P = .21$; [Figure 1](#)). When assessed as asthma phenotypes, East Asian children had a lower prevalence of nonatopic asthma (1.9%, 95% CI 0.7-5.1) compared with Caucasian children (4.5%, 95% CI 3.6-5.7) ($P = .096$), whereas the prevalence of atopic asthma was similar in both groups (8.9% vs 7.9%, $P = .607$).

An increase in prevalence of allergic disease was observed when comparing children with 1 versus 2 East Asian-born parents ([Figure E2](#), available in this article's [Online Repository at www.jaci-inpractice.org](http://www.jaci-inpractice.org)).

Furthermore, among East Asian infants with eczema, food allergy, or both at age 1, 12.8% (95% CI 8.1-19.6) had asthma at age 6, compared with 17.8% (95% CI 15.0-20.9) of Caucasian infants with eczema, food allergy or both at age 1 ($P = .165$).

Relationship between aeroallergen sensitization and asthma

The overlap between aeroallergen sensitization and asthma in Caucasian and East Asian children is shown in [Figure 2](#). Overall, 70% of East Asian children had either aeroallergen sensitization and/or asthma compared with only 41% of Caucasian children.

This was due to a high prevalence of aeroallergen sensitization in the East Asian group. However, fewer of the aeroallergen-sensitized East Asian children also had asthma compared with the aeroallergen-sensitized Caucasian children (15% vs 24%, $P = .01$).

Associations between early life eczema and food allergy status and asthma at age 6

[Table II](#) shows the relationship between infantile food allergy and eczema and diagnosed asthma at age 6 years. Caucasian children with both eczema and food allergy at age 1 were 3 times as likely to have asthma at age 6 compared with those with no eczema and no food allergy at age 1 (PR 3.56, 95% CI 2.72-4.67, $P < .001$). The magnitude of association was similar in East Asian children (PR 3.12, 95% CI 1.21-8.08, $P = .019$). There was no evidence that the association between food allergy and eczema status at age 1 and asthma at age 6 differed by ancestry. The associations observed in each ancestry group were broadly similar after excluding children with a history of wheeze in the first year of life, although the association seen in children with eczema alone was reduced ([Table II](#)).

Caucasian children with food allergy or eczema alone were twice as likely to have asthma at age 6. Food allergy alone remains associated with asthma after excluding Caucasian children with a history of wheeze ([Table II](#)). These findings were not observed in East Asian children.

Similar results were observed in a sensitivity analysis that included sampling weights to adjust for differences in those lost to follow-up compared with those who participated at age 6 years (see [Table E1](#), available in this article's [Online Repository at www.jaci-inpractice.org](http://www.jaci-inpractice.org)), as well as in sensitivity analyses using broader definitions of asthma (see [Table E2](#), available in this article's [Online Repository at www.jaci-inpractice.org](http://www.jaci-inpractice.org)) and

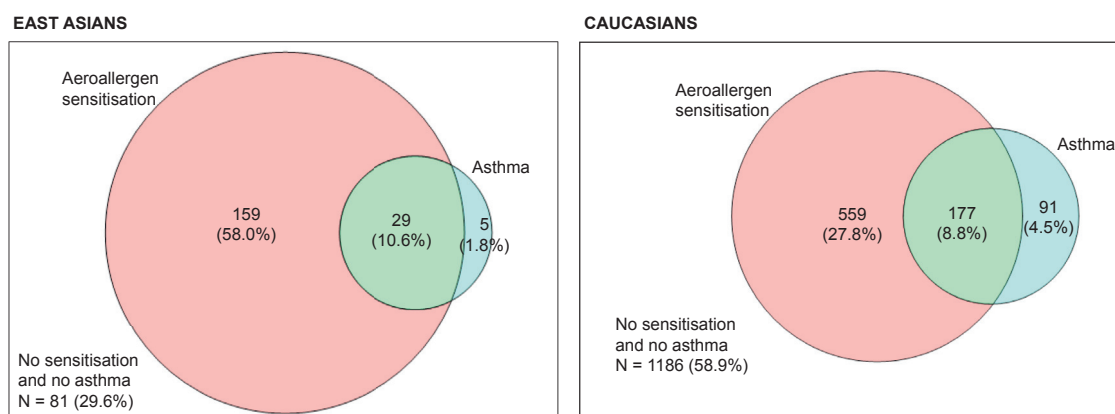


FIGURE 2. Aeroallergen sensitization and asthma at age 6 years in children with East Asian-born parents ($n = 274$) and Caucasian-born parents ($n = 2013$).

TABLE II. Association between food allergy and eczema at 1 y with asthma at 6 y of age, stratified by ancestry

TABLE II: Association between food allergy and eczema at 4 y with asthma at 6 y of age, stratified by ancestry										
Variable	Caucasian (n = 2620)				East Asian (n = 352)				P interaction	
	Total	Asthma (%)	PR* (95% CI)	P value	Total	Asthma (%)	PR* (95% CI)	P value		
All infants										
No eczema or food allergy	1662	151 (9.1)	1.0	—	135	8 (6.0)	1.0	—	—	
Food allergy only	92	21 (22.8)	2.45 (1.62-3.71)	<.001	24	3 (12.5)	1.89 (0.49-7.37)	.357	.966	
Eczema only	464	63 (13.6)	1.46 (1.11-1.92)	.007	71	5 (7.0)	1.14 (0.37-3.49)	.816	.788	
Eczema and food allergy	154	52 (33.8)	3.56 (2.72-4.67)	<.001	49	12 (24.5)	3.12 (1.21-8.08)	.019	.874	
Excluding infants wheezing during first year of life										
No eczema or food allergy	1276	103 (8.1)	1.0	—	105	8 (7.6)	1.0	—	—	
Food allergy only	73	15 (20.6)	2.52 (1.55-4.11)	<.001	20	2 (10)	1.36 (0.28-6.54)	.699	.584	
Eczema only	326	34 (10.4)	1.28 (0.89-1.85)	.184	47	0	Omitted [†]	—	—	
Eczema and food allergy	117	37 (31.6)	3.8 (2.74-5.28)	<.001	29	9 (31)	3.5 (1.26-9.69)	.016	.983	

CI, Confidence interval.

*Prevalence ratio (PR) adjusted for sex, socioeconomic status, family history of allergic disease, and antibiotics use.

†Prevalence ratio could not be calculated because there were no children with asthma in this group.

ISAAC definitions (see Table E3, available in this article's Online Repository at www.jaci-inpractice.org).

Associations between early life eczema and food allergy status and allergic rhinitis at age 6

Among Caucasian children, those with both eczema and food allergy at age 1 were 4-fold more likely to have allergic rhinitis at age 6 compared with those with no eczema and no food allergy at age 1 (PR 4.26, 95% CI 2.97-6.11). Although the magnitude of this association was lower for Asian children (PR 2.29, 95% CI 1.1-4.8), there was only modest evidence that ancestry modified the association between food allergy and eczema status at age 1 and allergic rhinitis at age 6 (P interaction = .091, Table III). Food allergy alone was also associated with allergic rhinitis in both Caucasian and East Asian children, whereas eczema alone was only associated with allergic rhinitis in Caucasian children (Table III).

Similar results were observed in the sensitivity analyses (see Tables E1-E3, available in this article's Online Repository at www.jaci-inpractice.org), although the magnitude of some of the associations was attenuated.

DISCUSSION

We have shown through this study that East Asian children have a higher prevalence of most allergic diseases at 6 years of age. Asthma appears to be similar between East Asian and Caucasian children. However, there was no evidence of a differential progression of the atopic march in East Asian children compared with Caucasian children. Children with both IgE-mediated food allergy and eczema during infancy had an increased risk of allergic rhinitis and asthma at age 6, regardless of ancestry. Caucasian children with food allergy or eczema alone also had an increased risk of asthma and allergic rhinitis, although the magnitude of association was lower than those with both food allergy and eczema.

Our finding that asthma appears to follow a different pattern to other allergic diseases in East Asian children was unexpected. Sensitization to aeroallergens has been shown to be a strong risk factor for wheezing²⁴ and asthma.²⁵ However, although aeroallergen sensitization was twice as common in East Asian children, the prevalence of asthma was not similarly increased. Asthma was less common in East Asian children with aeroallergen sensitization compared with aeroallergen sensitized children of Caucasian parents. A previous study of 3 South East

TABLE III. Association between food allergy and eczema at 1 y with allergic rhinitis at 6 y of age, stratified by ancestry

Variable	Caucasian (n = 2620)				East Asian (n = 352)				P interaction
	Total	Allergic rhinitis (%)	PR* (95% CI)	P value	Total	Allergic rhinitis (%)	PR* (95% CI)	P value	
No eczema or food allergy	1190	76 (6.4)	1.0	—	95	11 (11.6)	1.0	—	—
Food allergy only	69	13 (18.8)	2.81 (1.67-4.74)	<.001	19	8 (42.1)	4.3 (2.19-8.42)	<.001	.688
Eczema only	333	51 (15.3)	2.16 (1.54-3.04)	<.001	55	13 (23.6)	1.64 (0.75-3.56)	.213	.559
Eczema and food allergy	114	34 (29.8)	4.26 (2.97-6.11)	<.001	41	13 (31.7)	2.29 (1.1-4.8)	.027	.091

CI, Confidence interval.

*Prevalence ratio (PR) adjusted for sex, socioeconomic status, and family history of allergic disease.

Asian populations also reported that the prevalence of asthma did not correspond well to the prevalence of atopy in these populations—despite differences in the prevalence of asthma between Hong Kong (7%), Kota Kinabalu, Malaysia (3%), and San Bu, China (2%), the prevalence of atopy (defined by positive SPT) in these countries was similar.²⁶ In the same study, Leung and Ho also found that family history was a stronger risk factor for asthma and allergic disease than aeroallergen sensitization in these 3 populations.

There are several possible explanations for the finding that asthma, unlike other allergic diseases, was not more common among East Asian children. Ethnic differences in lung function have been well documented across all ages.²⁷⁻³¹ Previous studies reported that, compared with Caucasians, South and North East Asians had reduced forced expired volume in 1 second (a measure of airway caliber) and forced vital capacity (a measure of lung size),²⁷ citing inspiratory muscle strength, lung compliance, or chest size as possible explanations for the differences.^{29,32,33} Lack of power to detect a difference is another potential issue, given that the prevalence of asthma was lower than other allergic diseases. Nevertheless, the marked differences observed between the 2 ancestry groups in terms of sensitization rates suggest that this is not the sole reason for the findings. In addition, non-differential misclassification (such as misclassification of viral wheeze as asthma) could reduce the magnitude of the association. Finally, it is possible that East Asian parents are less likely to recognize or seek medical diagnosis of asthma symptoms in their child. However, this latter possibility seems unlikely because the East Asian group was more often diagnosed with other allergic conditions, showing that this group was being seen in the health system. The reasons for this finding warrant further exploration.

Apart from asthma, other allergic diseases (IgE-mediated food allergy, eczema, aeroallergen sensitization, and allergic rhinitis) were very common in East Asian children. It has been proposed that the historical parasite endemic of the previous era shaped the evolution of the immune system in populations residing in tropical regions such as those in East Asia.³⁴ Genetic studies have shown correlations between geographical parasite prevalence and genetic diversity in genes involved in immune defense, and immune disease.³⁵ These signatures of genetic adaptation in the immune system point to regional endemic pathogen load as a strong selective pressure on human evolution. Theoretically, the selection of particular proinflammatory genotypes under historically high pathogen load may predispose to an “over-active” immune profile in modern environments, where many chronic infections have been eliminated and migration is common. This might contribute to the extremely high rates of allergy in East Asian children born into the westernized environment of

Australia. It has also been shown that age at migration is an important determinant for prescription of asthma medication, suggesting that environmental exposure in early life is critical.³⁶

Our findings add to current knowledge about the role of infant food allergy, primarily, IgE-mediated food allergy, separate from and in conjunction with eczema, in the atopic march. Previous studies have predominantly focused on eczema or food sensitization in early life, and studies of challenge-proven food allergy are limited.^{37,38} In addition, no previous studies have explored potential differences in the atopic march in children with different ethnic backgrounds. We also found several demographic differences, such as gender, pet ownership, and childcare attendance between Caucasians and East Asians, which may have contributed to differences in allergic disease prevalence between these groups. We have adjusted for these factors in our logistic regression models by including them as confounders if the magnitude of association between exposure and outcome changed by more than 10%.

One of the strengths of this study cohort is the high participation rate both at recruitment and at follow-up. Recruited participants are also broadly representative of the general population.¹¹ Furthermore, most food allergy studies are based on self-reported food allergy and an advantage of our study is the use of OFC to confirm food allergy status. Notwithstanding, our study does have some limitations. We found differences in several demographic and other characteristics for those lost to follow-up compared with those who participated in follow-up at age 6 years. To account for this participation bias, we adjusted for these differences using reweighting, which showed that our results remained consistent. It should also be noted that diagnosis of wheeze/asthma remains challenging at age 6. It is likely that some children may have continuing early transient wheeze or infectious induced symptoms. Atopic asthma, which generally becomes persistent, only occurred in a minority of patients (<5%). Moreover, the overall prevalence of asthma was low, which limits the likelihood of finding any association to ethnicity. Therefore, the negative finding for asthma requires further investigation. The follow-up of this cohort at age 10 years is currently underway and may shed more light on the issue. Our categorization for East Asians and Caucasians was based on parental country of birth that was used as a proxy for ancestry. Although some misclassification is likely using this definition, we have supporting evidence from our own study that self-reported ancestry correlates well with genetically inferred ancestry in this population.¹⁴ In addition, we have grouped all the East Asian countries together to increase statistical power, but there might be some differences between countries that we were unable to explore. We were also not powered to look at other Asian groups

such as the South Asians. Lastly, the lack of difference in association between food allergy and eczema status at age 1 and asthma diagnosis or allergic rhinitis at age 6 by ancestry may be due to the small sample size of East Asian children in the study.

CONCLUSIONS

High rates of allergy among East Asian children in infancy appear to be maintained into early childhood, with a high prevalence of eczema and allergic rhinitis at 6 years of age. Atopic asthma appears to be similar between East Asian and Caucasian children. Our findings identify East Asian children as a high-risk allergic group not just in infancy but throughout early childhood. We also showed that IgE-mediated food allergy and eczema in infancy increase the risk of asthma and allergic rhinitis in early childhood, irrespective of ancestry.

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ONLINE REPOSITORY

SENSITIVITY ANALYSIS TO EXPLORE THE
POTENTIAL IMPACT OF MISSING DATA

We have previously described differences in the characteristics of participants who completed the full questionnaire, the short questionnaire, and nonparticipants at age 4 years.^{E1} To mitigate potential bias in estimated prevalence ratios due to differential participation in follow-up, we generated sampling weights that were used to adjust (via rereighting) for differences in these factors between participants with and without missing data at age 6 years, using the inverse probability weighting method described by Little and Rubin.^{E2} Weights were calculated as the inverse of the pre-

dicted probability of inclusion at age 6 years, from a logistic regression model of participation including as covariates risk factors that were associated with completion of the full questionnaire rather than the short questionnaire or nonparticipation (the child's socioeconomic status, family history of allergy, parents' country of birth, whether or not the child had a challenge-confirmed food allergy at age 1 year, childcare attendance, infant formula use, dog ownership, maternal smoking during pregnancy, number of siblings, and child's eczema diagnosis at age 1 year). Essentially, we calculated a propensity score for each participant,^{E3} and these weights were included in the logistic regression models (see Table E1), with robust standard errors used to ensure that the precisions of estimated risks reflected the sample size.

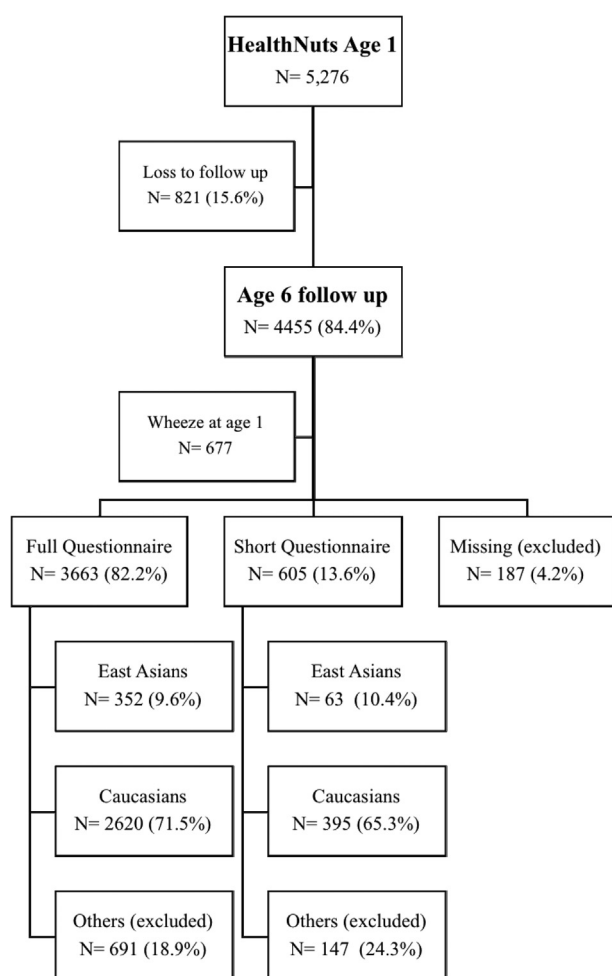


FIGURE E1. Flowchart of age 6 follow-up of the HealthNuts cohort.

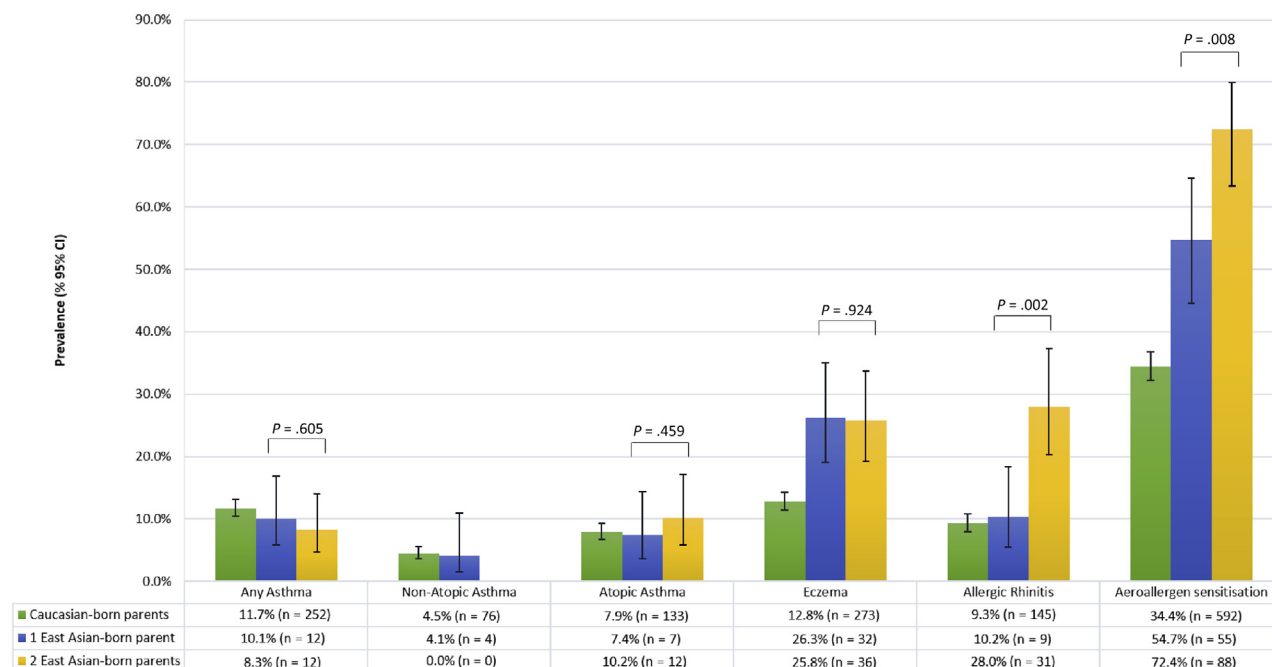


FIGURE E2. Weighted prevalence of allergic diseases, with 95% confidence interval, stratified by parental country of birth. *P* values shown are based on comparison between 1 and 2 East Asian-born parents. No *P* value is given for the nonatopic asthma group as there were no cases of nonatopic asthma among children with 2 East Asian-born parents.

TABLE E1. Sensitivity analysis—association between food allergy and eczema at 1 y and asthma and allergic rhinitis at age 6, with sampling weights included in the model

Sampling weights included in the model.					
Variable	Caucasian (n = 2620)		East Asian (n = 352)		P interaction
	PR (95% CI)	P value	PR (95% CI)	P value	
Asthma*					
No eczema or food allergy	1.0	—	1.0	—	
Food allergy only	2.25 (1.43-3.55)	<.001	2.62 (0.72-9.52)	.143	.788
Eczema only	1.3 (0.96-1.74)	.086	1.41 (0.45-4.38)	.552	.824
Eczema and food allergy	3.32 (2.49-4.43)	<.001	4 (1.52-10.52)	.005	.546
Allergic rhinitis*					
No eczema or food allergy	1.0	—	1.0	—	—
Food allergy only	2.79 (1.55-5.03)	.001	3.06 (1.36-6.9)	.007	.821
Eczema only	2.18 (1.51-3.14)	<.001	1.73 (0.8-3.75)	.166	.637
Eczema and food allergy	4.28 (2.88-6.38)	<.001	2.11 (0.95-4.69)	.068	.132

Factors included in reweighting were socioeconomic status, family history of allergy (eczema, food allergy, allergic rhinitis), parent's country of birth, infant's eczema diagnosis at age 1, infant's egg allergy status at age 1, infant's peanut allergy status at age 1, attendance at childcare, dog ownership, use of infant formula, number of siblings, and maternal smoking during pregnancy.

CI, Confidence interval; PR, prevalence ratio.

*Analyses were adjusted for sex.

TABLE E2. Sensitivity analysis—association between food allergy and eczema at age 1 and asthma and allergic rhinitis diagnosis at age 6 from a combined full and short questionnaire

from a combined full and short questionnaire					
Variable	Caucasian (n = 2620)		East Asian (n = 352)		P interaction
	PR (95% CI)	P value	PR (95% CI)	P value	
Asthma diagnosis*					
No eczema or food allergy	1.0	—	1.0	—	
Food allergy only	2.05 (1.37-3.05)	<.001	1.65 (0.48-5.65)	.422	.753
Eczema only	1.65 (1.32-2.07)	<.001	1.13 (0.43-2.96)	.801	.403
Eczema and food allergy	3.32 (2.61-4.21)	<.001	3.81 (1.72-8.47)	.001	.697
Allergic rhinitis diagnosis†					
No eczema or food allergy	1.0	—	1.0	—	
Food allergy only	1.91 (0.9-4.03)	.09	1.03 (0.38-2.82)	.953	.364
Eczema only	2.66 (1.91-3.71)	<.001	0.97 (0.47-1.99)	.932	.008
Eczema and food allergy	3.07 (1.92-4.91)	<.001	1.23 (0.6-2.52)	.564	.035

CI, Confidence interval; PR, prevalence ratio.

*Adjusted for sex, socioeconomic status, family history of allergic disease, and use of antibiotics.

†Adjusted for sex, socioeconomic status and family history of allergic disease.

TABLE E3. Sensitivity analysis—association between food allergy and eczema at 1 y and ISAAC questions on asthma and allergic rhinitis at age 6

at age 6					
Variable	Caucasian (n = 2620)		East Asian (n = 352)		P interaction
	PR (95% CI)	P value	PR (95% CI)	P value	
Wheeze*					
No eczema or food allergy	1.0	—	1.0	—	
Food allergy only	1.91 (1.36-2.68)	<.001	4.08 (1.61-10.38)	.003	.245
Eczema only	1.17 (0.94-1.47)	.162	1.52 (0.58-4)	.398	.57
Eczema and food allergy	2.87 (2.33-3.54)	<.001	3.16 (1.34-7.41)	.008	.521
Nose symptoms†					
No eczema or food allergy	1.0	—	1.0	—	
Food allergy only	1.33 (0.94-1.87)	.105	1.82 (1.11-2.99)	.018	.354
Eczema only	1.38 (1.17-1.64)	<.001	1.1 (0.68-1.76)	.698	.25
Eczema and food allergy	2.4 (2.01-2.87)	<.001	1.57 (1-2.46)	.052	.044

CI, Confidence interval; ISAAC, International Study of Asthma and Allergies in Childhood; PR, prevalence ratio.

*Wheeze was defined as any whistling in the chest or wheezing in the last 12 mo. Analysis was adjusted for sex, socioeconomic status, family history of allergic disease, and use of antibiotics.

†Nose symptoms defined as sneezing or runny/blocked nose when child did not have cold/flu in the last 12 mo. Analysis was adjusted for sex, socioeconomic status, and family history of allergic disease.

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