

Increased risk of peanut allergy in infants of Asian-born parents compared to those of Australian-born parents

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Abstract

Background: Asian infants appear to be over-represented among patients with clinical food allergy in Australia, but this has not been formally examined at the population level. Any difference in prevalence according to parental country of birth may be secondary to modifiable lifestyle factors. We aimed to quantify (i) differences in the prevalence of peanut allergy by parental country of birth and (ii) contribution of measured environmental exposures to these differences.

Methods: The population-based HealthNuts study in Melbourne, Australia, screened 5276 infants (74% participation) with skin prick tests and sensitized infants underwent food challenge. Of these, 535 had a parent born in East Asia and 574 in UK/Europe. Associations between parents' country of birth and offspring peanut allergy were examined using multiple logistic regression.

Results: Compared to infants with two Australian-born parents, peanut allergy was more common among infants with parent/s born in East Asia (OR 3.4, 95% CI 2.2–5.1) but not those with parent/s born in the UK/Europe (OR 0.8, 95% CI 0.4–1.5). Paradoxically rates of allergic disease were lower among Asian parents. A higher prevalence of eczema among infants of Asian parents explained around 30% of the increase in peanut allergy, while differences in dog ownership explained around 18%.

Conclusions: The high peanut allergy prevalence among infants of Asian-born parents appears to have occurred in a single generation and was not present among infants with parents migrating from other countries, suggesting gene–environment interactions are important. The role of eczema and microbial exposure in food allergy prevention warrants exploration.

Peanut allergy is becoming increasingly recognized as an important issue internationally, affecting around 1–3% of children in the USA, UK and Australia (1–3). By contrast, peanut allergy appears to be uncommon in Asian countries, although high-quality prevalence studies from this region are rare (4). Differences in peanut processing (5), consumption patterns (6) and environmental microbial exposures (7, 8) are among the hypotheses put forward to explain disparities in regional prevalence.

To date, few studies have investigated risk factors for peanut allergy, and as a result, these remain largely unknown. Both genetic and environmental factors appear to play a role (9). In an attempt to quantify the environmental component,

Du Toit and colleagues compared peanut allergy prevalence in two genetically similar populations living in different environments, namely Jewish children in the UK compared with Jewish children in Israel (6). Peanut allergy was more common in the UK, potentially due to different patterns of peanut consumption in infancy between the countries, although peanut consumption was not examined on an individual level. Environmental factors may also differentially affect individuals based on their genetic background (gene–environment interactions) (10). Studying the prevalence of peanut allergy among individuals growing up in broadly similar environments in terms of climate and overall microbial burden

with different genetic backgrounds has the potential to provide insights into the role of gene–environment interactions in peanut allergy, an area which has not previously been investigated.

Within a large population-based cohort of infants in Australia, we have previously reported that parents' country of birth was a risk factor for eczema and challenge-confirmed egg allergy (11, 12) although we did not assess whether this difference in prevalence was secondary to modifiable lifestyle factors. We extend that work here by examining peanut allergy, which is more likely than eczema and egg allergy to persist into later childhood and adulthood, as well as examining whether there are differential effects of risk factors based on genetic predisposition (as determined by parental country of birth as a proxy for genetic variation). In this study, we aimed to:

- 1 Quantify differences in the prevalence of infant food sensitization and food allergy, including peanut allergy, by parental country of birth.
- 2 Quantify the contribution of differences in measured environmental exposures to any differences in prevalence by parental country of birth identified in (1) above.
- 3 Identify any differences in predictors of peanut allergy by parental country of birth (potential gene–environment interactions).

Methods

HealthNuts study

The HealthNuts study is a population-based cohort of children recruited between September 2007 and August 2011. All infants aged between 11 and 15 months (inclusive) attending council-run immunization sessions for their 12-month immunizations were eligible for recruitment (mean age 12.7 months). Study methods have been described in detail elsewhere (1, 13). A sample size of 5000 was calculated to provide sufficient power to detect risk factors present in at least 10% of the population, given a prevalence of food allergy of 5–10%. For peanut allergy (prevalence 3% in this cohort), the sample size provides 92% power to detect a risk factor present in 10% of nonallergic individuals and 20% of peanut allergic individuals.

Briefly, infants were characterized for IgE-mediated food allergy status using skin prick test (SPT) screening to egg, peanut and sesame and shellfish ($n = 2405$; first half of the cohort) or cow's milk ($n = 2715$; second half of the cohort) at time of recruitment followed by oral food challenges (OFC) for infants sensitized to egg, peanut or sesame. Challenges were considered positive on development of objective symptoms (angioedema, ≥ 3 urticarial wheals persisting for at least 5 min, vomiting, wheeze or circulatory symptoms) within two hours of a dose of challenge food (14). At the time of challenge, blood samples were collected for measurement of specific IgE.

Ethics

Ethical approval was obtained from the Office for Children HREC (ref. no. CDF/07/492), Department of Human

Services HREC (ref. no. 10/07) and Royal Children's Hospital HREC (ref. no. 27047). All parents/guardians provided written informed consent.

Definitions

Outcomes

Food sensitization was defined as a SPT wheal size ≥ 2 mm to egg, peanut, sesame, shellfish (tested for the first 2405 infants recruited) or cow's milk (replaced shellfish in the allergen panel for the second half of the cohort; 2715 infants).

Food allergy to egg, peanut or sesame was defined as a positive oral food challenge in sensitized infants (SPT wheal ≥ 2 mm or specific IgE ≥ 0.35 ku/l).

Exposures

Maternal and paternal countries of birth were classified into ten regions (Table S2). Parents were also asked whether they had migrated into Australia in the past 5 years (yes/no). In a more intensive substudy of 300 infants attending challenge clinic, parental country of birth reflected ethnicity ($>90\%$ of parents born in Australia and Asia were Caucasian and Asian, respectively) and skin colour (15). Information on location of mother during pregnancy was also available for this subgroup, with more than 90% of pregnancies, and all births, occurring in Australia.

Infant history of eczema was defined as a parent report of a diagnosis of eczema in the infant at any time in the first 12 months of life.

Information on environmental exposures in the first year of life and family history of allergy were collected by parent-completed questionnaire prior to parents receiving the results of the skin prick test to reduce the potential for recall bias based on the outcome of food sensitization. Potential risk factors considered in the analysis were those previously associated with allergic disease in the HealthNuts cohort and in other literature, namely infant diet, factors related to microbial exposure and personal and family history of atopy (12).

Statistical methods

Group-specific prevalences of food sensitization and food allergy were estimated using observed proportions, with 95% confidence intervals for the corresponding population proportion generated by assuming a binomial sampling distribution for the number of participants with sensitization and allergy, respectively. We compared the prevalence of food sensitization and food allergy by parents' country of birth for those groups that made up at least 10% of the study population (Australia, the UK/Europe and East Asia). Infants were excluded from this analysis if both parents were born in different regions outside Australia ($n = 274$).

The magnitude of the association between the risk of food allergy and the risk factors parental country of birth, length of parental residence in Australia (<5 years *vs*

>5 years) and maternal vs paternal country of birth was quantified by estimating odds ratios from a logistic regression model.

To identify any differences in the magnitude of the association between exposures and the risk of infant allergic disease by parental country of birth, adjusted logistic regression models included interaction terms between parental country of birth and the exposures being considered, with *P*-values for the null hypothesis of no interaction calculated using the Wald test. Potential confounders were prematurity, mode of delivery, birthweight, maternal and household smoking, socio-economic status, family

history of allergy, infant history of eczema, dog ownership, age at first egg introduction and number of siblings and these factors were included in the model if they altered the magnitude of the odds ratio for the association between the exposure of interest and the risk of food allergy by more than 10%. As the number of associations considered in this paper is relatively low in the context of modern genetic association studies, we have not adjusted formally for multiple comparisons. We do, however, quote *P*-values infrequently in the paper and do not rely on significance testing or accepting/rejecting null hypotheses to form any of our conclusions.

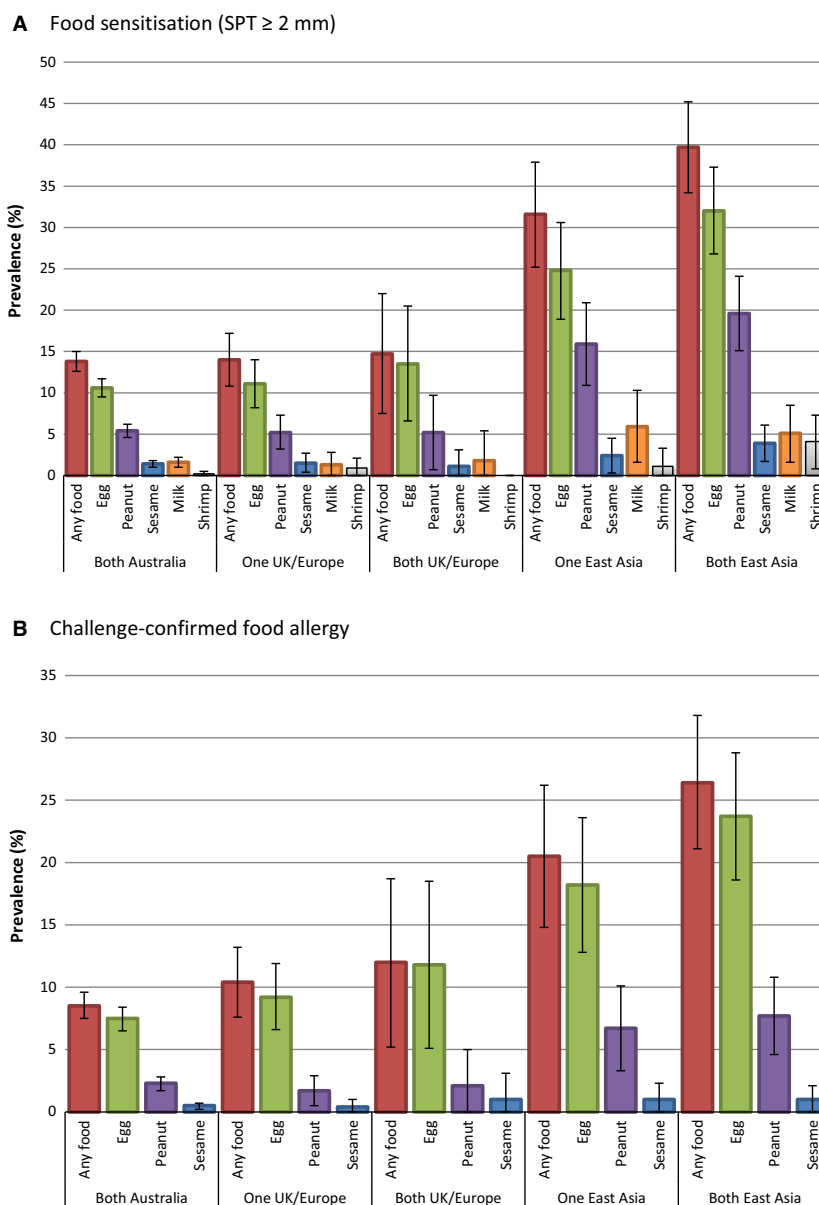


Figure 1 Prevalence of food sensitization and allergy (with 95% CI) by parents' country of birth. (a) Food sensitization (SPT ≥ 2 mm). (b) Challenge-confirmed food allergy.

Table 1 Prevalence (%) of potential risk factors for food allergy among infants with parents born in Australia compared with infants with parents born in East Asia

	Both Australia (baseline)	East Asia		
		One parent	Both parents	P*
Family and infant characteristics				
Household smoking	23.1	19.2	18.7	0.10
Maternal smoking during pregnancy	5.9	0.9	0.3	<0.001
SEIFA Disadvantage Index (mean) [†]	1048.5	1052.4	1042.5	0.41
Birthweight (grams, mean)	3439.5	3214.5	3199.6	<0.001
Caesarean section delivery	33.4	37.8	29.5	0.13
Male sex	50.3	55.3	55.1	0.12
Infant diet				
Egg introduced				
<10 months	63.1	64.6	67.7	0.27
≥10 months	36.9	35.4	32.3	
Peanut introduced				
<10 months	11.0	7.3	9.3	0.18
≥10 months	89.0	92.7	90.8	
Eaten sesame	25.7	34.1	37.7	<0.001
Duration of breastfeeding				
<1 month	15.0	9.4	7.9	<0.001
1–6 months	28.5	28.2	36.1	
7–12 months	28.6	22.1	18.4	
>12 months	27.9	40.4	37.7	
Use of infant formula	79.4	80.5	85.1	0.062
Type of formula				
Cow's milk	84.5	87.8	88.5	0.17
Partially hydrolysed	15.5	12.2	11.5	
Other environmental exposures				
Antibiotic use	51.5	49.1	42.0	0.006
Any siblings	51.4	42.0	45.3	0.005
Childcare attendance				
None	71.0	76.0	80.5	0.001
Started after 6 months of age	21.6	14.8	13.5	
Started before 6 months of age	7.4	9.2	6.1	
Dog in the household	39.5	19.6	8.5	<0.001
Cat in the household	20.5	9.1	4.1	<0.001
Personal and family history of atopy				
Infant history of eczema	25.3	33.2	47.2	<0.001
Maternal history of any allergy	48.9	44.3	33.2	<0.001
Maternal history of asthma	17.1	10.1	8.9	<0.001
Maternal history of hay fever	33.8	35.2	22.5	<0.001
Maternal history of eczema	15.9	12.3	9.2	0.004
Maternal history of food allergy	6.0	5.5	3.5	0.18
Maternal history of peanut allergy	0.7	0.9	0.0	0.30
Paternal history of allergy	41.2	45.7	39.6	0.35
Paternal history of asthma	15.8	17.8	6.3	<0.001
Paternal history of hay fever	29.1	32.4	32.9	0.25
Paternal history of eczema	8.5	11.4	6.7	0.15
Paternal history of food allergy	3.9	5.5	3.2	0.39
Paternal history of peanut allergy	0.7	0.5	0.0	0.31
Any parental history of allergy	69.1	65.3	54.1	<0.001
Sibling history of allergy [‡]	40.4	48.9	44.8	0.18

**P*-values calculated from chi-square test comparing infants with one or both parents born in East Asia with baseline (both parents born in Australia, values in italics).

[†]Socio-economic status was assigned on the basis of home postcode by using Socio-Economic Indexes for Areas (SEIFA) measures derived from the 2006 Australian census, which assess relative socio-economic advantage/disadvantage, economic resources (income, assets and expenditure), and educational and occupational characteristics (24).

[‡]Among those with siblings.

The contribution of differences in measured exposures between infants with Australian-born and Asian-born parents to different prevalence rates was calculated by comparing the odds ratio for the association between parents' country of birth and food allergy before and after adjustment for these exposures. The baseline risk was the OR for food allergy for those having one or both parents born in Asia compared with both parents born in Australia (OR_b). The model was extended by the addition in turn of each of the individual exposures generating an adjusted risk for parents' country of birth (OR_a). The contribution of differences in prevalence of each risk factor to the higher food allergy prevalence in infants of parents born in Asia was estimated as $([1 - \text{OR}_b] - [1 - \text{OR}_a]) / [1 - \text{OR}_b]$, which is a measure of the proportionate decline in the excess risk (16).

Results

Study participation

Of 7134 eligible infants, 5276 participated (74%). Sensitization and food allergy data were available for 5199 and 4843 infants, respectively. Complete information on parents' country of birth and all relevant environmental exposures was available for 4063 infants (Figure S1).

Prevalence of food sensitization and allergy according to parents' country of birth

The prevalence of peanut sensitization among infants with both parents born in Australia was 5.4%, increasing to

Table 2 Relationship between potential risk factors and food allergy, stratified by parent's country of birth

	Peanut allergy			Egg allergy		Any food allergy	
	Both parents born in Australia	One or both born in East Asia	<i>P</i> interaction	Both parents born in Australia	One or both born in East Asia	Both parents born in Australia	One or both born in East Asia
Model 1: Infant diet							
Delayed egg introduction (after 10 months)	0.9 (0.4, 1.9)	1.6 (0.6, 4.4)	0.59	1.4 (1.0, 2.2)	2.0 (1.0, 4.1)	1.4 (1.0, 2.1)	2.1 (1.1, 4.2)
Delayed peanut introduction (after 10 months)	1.4 (0.3, 6.3)	0.1 (0.02, 1.1)	0.15	1.2 (0.5, 2.8)	0.8 (0.1, 4.1)	1.4 (0.6, 3.3)	0.9 (0.2, 4.9)
Eaten sesame	1.0 (0.4, 2.6)	0.5 (0.2, 1.8)	0.90	0.6 (0.4, 1.1)	1.3 (0.6, 2.7)	0.7 (0.4, 1.2)	1.3 (0.6, 2.7)
Duration of breastfeeding							
0–6 month	1.0	1.0	0.48	1.0	1.0	1.0	1.0
7–12 months	0.4 (0.1, 1.3)	0.8 (0.2, 3.2)		1.3 (0.8, 2.2)	1.1 (0.4, 2.8)	1.2 (0.7, 1.9)	0.8 (0.3, 2.1)
>12 months	1.9 (0.7, 5.4)	2.3 (0.8, 6.9)		1.7 (0.9, 3.1)	1.8 (0.8, 3.9)	1.6 (0.9, 2.8)	1.6 (0.7, 3.5)
Type of formula							
None	1.0	1.0	0.95	1.0	1.0	1.0	1.0
Cow's milk	2.0 (0.6, 6.4)	2.8 (0.6, 13.3)		1.1 (0.6, 2.0)	2.2 (0.8, 6.7)	1.1 (0.6, 2.0)	2.1 (0.7, 13.5)
Partially hydrolysed	0.5 (0.05, 4.8)	1.0 (0.07, 12.2)		1.2 (0.6, 2.8)	2.1 (0.5, 8.5)	1.2 (0.5, 2.5)	1.8 (0.4, 7.2)
Model 2: Other environmental exposures							
Antibiotic use	0.7 (0.4, 1.3)	1.2 (0.5, 2.6)	0.36	1.2 (0.9, 1.6)	0.9 (0.5, 1.5)	1.2 (0.9, 1.6)	0.8 (0.5, 1.4)
Number of siblings	1.1 (0.8, 1.7)	0.9 (0.5, 1.8)	0.53	0.7 (0.5, 0.9)	0.9 (0.6, 1.4)	0.8 (0.6, 1.0)	0.9 (0.6, 1.4)
Childcare attendance	1.3 (0.7, 2.4)	0.2 (0.04, 0.8)	0.023	1.1 (0.9, 1.5)	0.5 (0.3, 1.1)	1.1 (0.8, 1.5)	0.5 (0.2, 1.0)
Dog ownership	0.4 (0.2, 0.7)	0.9 (0.2, 3.2)	0.09	0.7 (0.5, 1.0)	0.7 (0.3, 1.8)	0.7 (0.5, 1.0)	0.8 (0.3, 1.9)
Cat ownership	0.7 (0.4, 3.0)	2.5 (0.6, 9.6)	0.03	0.7 (0.4, 1.0)	1.1 (0.4, 3.6)	0.7 (0.5, 1.1)	1.6 (0.6, 4.8)
Model 3: Personal and family history of allergy							
Infantile eczema in first year of life (diagnosis)	8.7 (4.8, 15.8)	6.6 (2.7, 16.0)	0.62	5.0 (3.7, 6.8)	3.8 (2.2, 6.4)	5.1 (2.8, 6.9)	4.1 (2.4, 6.8)
Maternal history of allergy	1.2 (0.7, 2.0)	1.2 (0.6, 2.7)	0.57	1.6 (1.2, 2.2)	1.1 (0.6, 1.8)	1.5 (1.1, 2.1)	1.1 (0.7, 1.9)
Paternal history of allergy	0.8 (0.4, 1.3)	2.5 (1.1, 5.4)	0.012	1.2 (0.9, 1.6)	1.8 (1.0, 3.0)	1.1 (0.8, 1.5)	1.8 (1.1, 3.1)
Sibling history of allergy	1.2 (0.6, 2.4)	1.4 (0.5, 4.1)	0.93	1.7 (1.1, 2.6)	1.7 (0.8, 3.6)	1.5 (1.0, 2.2)	1.6 (0.8, 3.2)

Model 1: Additionally adjusted for infant history of eczema, number of siblings and family history of allergy.

Model 2: Additionally adjusted for infant history of eczema, number of siblings, age at first egg introduction, family history of allergy, socioeconomic status (defined by SEIFA of postcode) and household smoking.

Model 3: Additionally adjusted for number of siblings, dog ownership and age at first egg introduction.

Bold: Evidence for an association with food allergy ($P < 0.05$).

Table 3 Contribution of individual risk factors to difference in food allergy prevalence between infants of Australian and Asian-born parents

Factor	Percentage contribution*		
	Peanut allergy	Egg allergy	Any food allergy
Infantile eczema	33.3	21.1	21.6
Dog ownership	17.7	11.9	10.1
Increasing duration of breastfeeding	9.6	2.9	4.0
Sibling history of allergy	3.1	-0.8	-1.0
Cat ownership	0.0	4.9	3.9
Antibiotic use	-1.0	-3.0	-2.9
Eaten sesame	-1.1	3.8	-1.9
Egg introduction after 10 months of age	-1.5	-6.4	-5.7
Maternal history of allergy	-9.3	-14.7	-13.6

*Defined as the proportionate decline in the excess risk of food allergy attributed to having parents born in Asia when each factor was individually adjusted for in the analysis.

15.9% among those with one parent born in East Asia and 19.6% among those with both parents born in East Asia (P trend <0.001). Peanut allergy was found in 2.3% of infants with both parents born in Australia, compared with 6.7% of infants those with one parent born in East Asia and 7.7% of infants with both parents born in East Asia (P trend <0.001). The magnitude of the association between parents' country of birth and both sensitization (Fig. 1a) and challenge-confirmed allergy (Fig. 1b) was similar for all measured foods (Table S1) and was similar for parents born in North-East Asia and South-East Asia (Table S3).

There was no evidence that infants with parents born in the UK or Europe had a higher risk of any food allergy than those with parents born in Australia (Table S1).

There was no evidence of a difference in peanut allergy risk depending on whether the Asian-born parent was the mother or father of the child (OR 0.8, 95% CI 0.2, 2.6, $P = 0.72$ for father vs mother) or length of parental residence in Australia (>5 years 8.6% vs <5 years 6.3%, $P = 0.47$).

Characteristics of infants with parents born in Australia and Asia are shown in Table 1.

Factors that predict food allergy by parents' country of birth

The majority of factors examined had a similar magnitude of effect on risk of peanut allergy in the infant irrespective of parents' country of birth (Table 2). Childcare attendance was associated with a lower odds of peanut allergy only among infants with one or more parents born in Asia (P interaction = 0.023). This might be partially explained by differences in childcare attendance patterns according to parents' country of birth: infants with Asian-born parents attending childcare were more likely to have started before 6 months of age (32% vs 24%, $P = 0.07$) and were more likely to attend for at least 3 days per week (25.7% vs 50%, $P < 0.001$). Paternal history of allergy was also associated with peanut allergy risk only among infants with parents born in Asia.

Contribution of individual risk factors to the difference in prevalence

The largest contribution towards explaining the difference in peanut allergy prevalence between infants of Australian-born and Asian-born parents was from infantile eczema (Table 3).

Of the measured environmental factors, dog ownership explained the greatest proportion of the difference in prevalence

Table 4 Multivariate logistic regression model of association between parents' country of birth and food allergy, adjusted for infant history of eczema and environmental factors that contributed to the difference in food allergy prevalence according to parents' country of birth

Parents' country of birth/food allergy outcome	Unadjusted		Adjusted for infant history of eczema		Adjusted for other confounding factors*	
	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
Peanut allergy						
Both Australia ($n = 3023$)	1.0		1.0		1.0	
One Asia ($n = 219$)	3.1 (1.7, 5.6)	<0.001	2.6 (1.3, 5.0)	0.005	2.8 (1.5, 5.1)	0.001
Both Asia ($n = 316$)	3.6 (2.2, 5.9)	<0.001	2.8 (1.7, 4.7)	<0.001	3.1 (1.8, 5.1)	<0.001
Egg allergy						
Both Australia ($n = 3023$)	1.0		1.0		1.0	
One Asia ($n = 219$)	2.8 (1.9, 4.0)	<0.001	2.3 (1.5, 3.5)	<0.001	2.6 (1.7, 3.8)	<0.001
Both Asia ($n = 316$)	3.8 (2.8, 5.3)	<0.001	3.3 (2.4, 4.7)	<0.001	3.5 (2.5, 4.8)	<0.001
Any food allergy						
Both Australia ($n = 3023$)	1.0		1.0		1.0	
One Asia ($n = 219$)	2.8 (1.9, 4.0)	<0.001	2.3 (1.5, 3.5)	<0.001	2.6 (1.8, 3.8)	<0.001
Both Asia ($n = 316$)	3.9 (2.8, 5.2)	<0.001	3.4 (2.4, 4.7)	<0.001	3.5 (2.6, 4.8)	<0.001

*Defined as those environmental factors that altered the magnitude of the odds ratio for the association between parents' country of birth and food allergy by more than 10%. In all cases, dog ownership was the only factor which met this criterion.

of peanut allergy (Table 3). Type of infant formula used, timing of peanut introduction, paternal history of allergy, number of siblings and childcare attendance each explained less than 3% of the difference in peanut, egg and any food allergy. Infants of Asian-born parents were more likely to be peanut allergic even after adjusting for eczema and environmental factors (Table 4).

Discussion

In a large population-based study with high participation rates and standardized measurement of food allergy outcomes, we found that sensitization and challenge-confirmed allergy to peanut were around three times more common in infants with parents born in East Asia compared to those with parents born in Australia. The difference in peanut allergy prevalence was not completely explained by differences in modifiable lifestyle factors such as infant feeding practices and exposures to pets or other children, although lower rates of dog ownership among infants of East Asian parents appeared to contribute to some of the increase in peanut allergy.

Previous studies have suggested that early introduction of allergenic foods may contribute to a lower prevalence of food allergy in genetically similar populations living in different countries (6). In this cohort, introduction of peanut into the infant diet before 10 months of age was rare irrespective of parental country of birth and did not contribute substantially to differences in peanut allergy prevalence. Household peanut consumption was not measured within this study, and the potential role of transcutaneous nut exposure as a consequence of household peanut consumption (17) in explaining differences in peanut sensitization between infants of Asian and Australian-born parents warrants further exploration. A higher prevalence of eczema among infants of Asian parents explained around 30% of the increase in peanut allergy. This may be due to shared environmental or genetic risk factors for food allergy and eczema. If sensitization to peanut occurs through a damaged skin barrier secondary to eczema as has previously been suggested (9), it also suggests that up to 30% of peanut allergy may be preventable if eczema in infancy can be prevented through use of barrier creams or other methods (18).

It has been hypothesized that populations whose immune system has adapted to a tropical environment with more parasitic disease might deviate towards an allergic response when relocating to an environment with less microbial exposure (19). Alternatively, lower mean annual relative humidity and UV index in Melbourne compared to East Asian countries such as Singapore, Vietnam and Thailand could contribute to the higher prevalence of both eczema and food allergy in infants of Asian parents (20). This may increase skin barrier impairment in genetically susceptible individuals which may lead to increased exposure to allergens through the skin and therefore increased peanut sensitization. Consistent with this hypothesis, individuals with a damaged skin barrier secondary to filaggrin gene mutations have been found to be at increased risk of food sensitization, and

consequently food allergy, in this cohort and other studies internationally (21, 22).

The increased risk of allergic disease in Australian-born infants of Asian-born parents appears to have occurred in a single generation, with the prevalence of reported allergic disease similar or even lower in Asian-born parents themselves compared with Australian-born parents. Furthermore, the increased risk of peanut allergy appeared to be specific to infants of Asian parents and was not seen among infants of parents born in the UK or Europe. Together, these findings suggest that environmental exposures of infants growing up in Australia have a differential effect according to genetic background (gene–environment interactions). Although Asian parents may also be genetically at risk of allergy, a protective effect of microbial exposure, more humid climate or more vitamin D exposure in early life may prevent the expression of their genetic susceptibility.

Overall, few of the examined factors had a differential effect on peanut allergy or food allergy according to parental country of birth. Childcare attendance appeared to be protective only among infants of Asian parents, although this could reflect differences in childcare practices in this group (earlier and more frequent attendance). We have also previously reported that the relationship between vitamin D insufficiency and food allergy may differ by parental country of birth (15).

The HealthNuts study design has several strengths for investigating the relationship between parental country of birth and infant food allergy. These include the use of standardized objective food allergy testing for all participants (by skin prick test and food challenge), which avoids the potential for diagnostic bias or reporting bias for allergic disease by ethnicity (23). The large sample size provides precision in measures of food allergy prevalence in subgroups defined by parental country of birth. Potential limitations of this study include the potential for participation bias; however, this is mitigated by high response rates (74%), including among infants of non-Australian parents. Only 5% of potential participants were excluded because parents did not speak English. The proportion of Australian-born mothers is similar in HealthNuts compared with the general population of Victoria (13); thus, our findings are likely to be generalizable to the wider population. Selection bias is an unlikely explanation for our findings as Asian-born parents were slightly over-represented in the study cohort, and nonresponders were at lower risk for food allergy as we have previously described (1). Taking into account nonparticipation by Australian-born parents due to low food allergy risk in infants may have slightly increased the magnitude of the higher food allergy prevalence among infants of Asian-born parents. Using parental country of birth as a proxy for genetic variation also has limitations, although correlation with self-reported ethnicity was high in this cohort.

Conclusion

High peanut allergy rates among infants of Asian-born parents appear to have occurred in a single generation and are unlikely to be explained by differences in timing of introduction of

peanut or exposure to potentially protective environmental factors such as pets or other children. Further characterization of environmental changes occurring postmigration from Asia to Australia and the interaction of these factors with genetic background have the potential to provide novel insights into factors driving peanut allergy development.

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Author contributions

KJA, LCG, SCD, MLKT, A-LP and DH contributed to conception and design of the HealthNuts study. JJK and RLP conducted the data analysis, and JJK was responsible for the first draft of the article. All authors contributed to interpretation of the data, revision of the draft manuscript and approved the final version to be published.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Flow chart of study participation, follow up and reasons for missing data.

Table S1. Association between parents' country of birth and food sensitisation (SPT ≥ 2 mm) and challenge-confirmed food allergy.

Table S2. Classification of parents' region of birth.

Table S3. Prevalence of infantile food allergy stratified by parent's country of birth.

Table S4. Country of birth of parents born in East Asia, by number of parents born in East Asia and length of residence in Australia.

- insufficiency is associated with challenge-proven food allergy in infants. *J Allergy Clin Immunol* 2013;**131**:1109–1116.
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Supporting information:

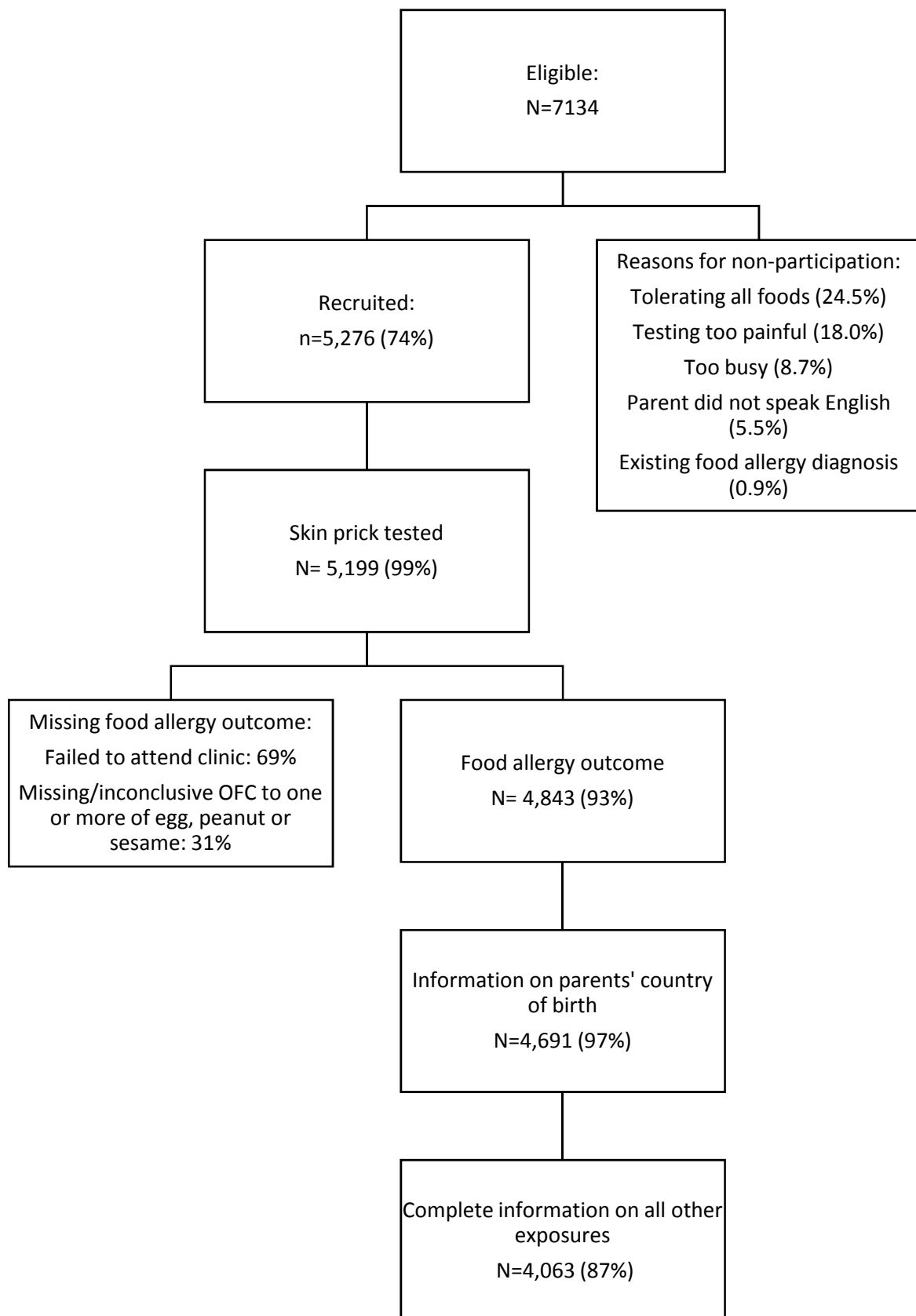


Figure S1: Flow chart of study participation, follow up and reasons for missing data

		Parents' country of birth				
		Both Australia (n=3023)	One UK/Europe (n=474)	Both UK/ Europe (n=100)	One East Asia (n=219)	Both East Asia (n=316)
Any food						
Sensitisation (n=892)	OR (95% CI)	1.0 (baseline)	1.0 (0.8, 1.4)	1.1 (0.6, 1.9)	2.9 (2.1, 3.9)	4.1 (3.2, 5.3)
	P value		0.90	0.80	<0.001	<0.001
Allergy (n=534)	OR (95% CI)	1.0 (baseline)	1.2 (0.9, 1.7)	1.5 (0.8, 2.8)	2.8 (1.9, 4.0)	3.9 (2.8, 5.2)
	P value		0.20	0.25	<0.001	<0.001
Peanut						
Sensitisation (n=390)	OR (95% CI)	1.0 (baseline)	1.0 (0.6, 1.5)	1.0 (0.4, 2.4)	3.3 (2.2, 4.9)	4.2 (3.1, 5.9)
	P value		0.85	0.93	<0.001	<0.001
Allergy (n=156)	OR (95% CI)	1.0 (baseline)	0.8 (0.4, 1.6)	0.9 (0.2, 3.8)	3.1 (1.7, 5.6)	3.6 (2.2, 5.9)
	P value		0.47	0.90	<0.001	<0.001
Egg						
Sensitisation (n=693)	OR (95% CI)	1.0 (baseline)	1.1 (0.8, 1.4)	1.3 (0.7, 2.4)	2.8 (2.0, 3.9)	4.0 (3.0, 5.2)
	P value		0.76	0.36	<0.001	<0.001
Allergy (n=468)	OR (95% CI)	1.0 (baseline)	1.3 (0.9, 1.8)	1.7 (0.9, 3.2)	2.8 (1.9, 4.0)	3.8 (2.8, 5.3)
	P value		0.19	0.12	<0.001	<0.001
Sesame						
Sensitisation (n=96)	OR (95% CI)	1.0 (baseline)	1.1 (0.5, 2.5)	0.8 (0.1, 5.6)	1.8 (0.7, 4.6)	3.0 (1.5, 5.7)
	P value		0.78	0.79	0.23	0.001
Allergy (n=33)	OR (95% CI)	1.0 (baseline)	0.9 (0.2, 4.0)	2.2 (0.3, 16.8)	2.0 (0.5, 8.9)	2.1 (0.6, 7.4)
	P value		0.91	0.45	0.36	0.25
Cow's milk*						

Sensitisation (n=60)	OR (95% CI)	1.0 (baseline)	0.8 (0.3, 2.8)	1.1 (0.2, 8.6)	3.9 (1.7, 9.3)	3.3 (1.5, 7.5)
	P value		0.78	0.90	0.002	0.004
Allergy (n=30)	OR (95% CI)	1.0 (baseline)	1.0 (0.2, 4.4)	ND**	2.9 (0.8, 10.4)	2.9 (1.0, 9.0)
	P value		0.99		0.094	0.061

Shellfish

Sensitisation (n=14)	OR (95% CI)	1.0 (baseline)	3.9 (0.6, 23.5)	ND**	5.1 (0.5, 49.2)	19.0 (4.7, 77.0)
	P value		0.14		0.16	<0.001

*Restricted to the 2715 infants with a SPT to cow's milk at baseline (n=60 had a SPT $\geq$ 2mm). Cow's milk allergy was defined as a parent-reported reaction to milk in the context of a SPT $\geq$ 2mm (n=30/2715).

**Not determined – no infants with both parents born in the UK/Europe were defined as cow's milk allergic or had a SPT $\geq$ 2mm to shrimp

Table S2: Classification of parents' region of birth

Region†	Countries included in the region*
Australia	Australia
East Asia	Brunei, Burma, Cambodia, China, Hong Kong, Indonesia, Japan, Korea, Laos, Macau, Malaysia, Myanmar, Papua New Guinea, Philippines, PR China, Singapore, South Korea, Taiwan, Thailand, Vietnam.
<i>North East Asia</i>	<i>China, Hong Kong, Macau, Taiwan, Japan, North Korea, South Korea</i>
<i>South East Asia</i>	<i>Cambodia, Laos, Thailand, Vietnam, Indonesia, Malaysia, Philippines, Singapore and Timor-Leste</i>
South Asia	Bangladesh, India, Nepal, Pakistan, Sri Lanka.
Middle East	Afghanistan, Bahrain, Dubai, Iran, Iraq, Israel, Jordan, Kuwait, Lebanon, Palestine, Syria, Turkey.
Africa	Algeria, East Africa, Egypt, Eritrea, Ethiopia, Ghana, Kenya, Libya, Mali, Mauritius, Morocco, Mozambique, Namibia, Nigeria, Sierra Leone, Somalia, South Africa, Sudan, Zambia, Tanzania, Uganda, Zimbabwe.
North America	Canada, Mexico, USA ('America').
South America	Argentina, Brazil, Chile, Colombia, El Salvador, Peru, South America, Venezuela.
Oceania	Cook Islands, Fiji (Fiji Islands), New Zealand, Samoa, Solomon Islands, Tonga.
United Kingdom & Ireland	Britain England, Ireland, Northern Ireland, Republic of Ireland, Scotland, UK, Wales.
Europe	Albania, Austria, Belgium, Bosnia, Croatia, Cyprus, Czechoslovakia, Czech Republic, Denmark, Finland, Former USSR, France, Germany, Greece, Holland, Hungary, Italy, Kosova, Lithuania, Macedonia, Malta, The Netherlands, Norway, Poland, Portugal, Romania, Russia, Serbia, Slovakia, Slovenia, Spain, Sweden, Switzerland, Ukraine, USSR, Yugoslavia.

*Countries as listed in HealthNuts questionnaires

† Groupings based on the Standard Australian Classification of Countries (SACC) which were developed to be relevant to Australia's multicultural society for use in analysing Australian-based country of origin data

(<http://www.abs.gov.au/AUSSTATS/abs@.nsf/Lookup/1269.0Main+Features12011?OpenDocument>). Groups in the SACC comprise geographically proximate countries which have broadly similar social, cultural, economic and political characteristics.

Table S3: Prevalence of infantile food allergy stratified by parent's country of birth

	Any food allergy	OR (95% CI)	P
Both Australia (n=3023)	8.5%	1.0 (baseline)	-
One UK (n=307)	10.9%	1.3 (0.9, 1.9)	0.17
Both UK (n=55)	15.4%	1.9 (0.9, 4.2)	0.087
One Europe (n=167)	9.4%	1.1 (0.6, 1.9)	0.71
Both Europe (n=45)	7.5%	0.9 (0.3, 2.8)	0.82
One Mid East (n=76)	16.7%	2.1 (1.1, 4.0)	0.018
Both Mid East (n=62)	5.7%	0.6 (0.2, 2.1)	0.46
One Africa (n=70)	4.4%	0.5 (0.2, 1.6)	0.24
Both Africa (n=57)	11.5%	1.4 (0.6, 3.3)	0.45
One South America (n=45)	13.2%	1.6 (0.6, 4.2)	0.32
Both South America (n=11)	11.1%	1.3 (0.2, 10.8)	0.78
One North America (n=78)	11.8%	1.4 (0.7, 2.9)	0.31
Both North America (n=5)	0.0%	ND	-
One Oceania (n=165)	13.9%	1.7 (1.1, 2.8)	0.021
Both Oceania (n=53)	12.5%	1.5 (0.6, 3.6)	0.33
One South Asia (n=31)	14.8%	1.9 (0.6, 5.4)	0.25
Both South Asia (n=39)	5.4%	0.6 (0.1, 2.6)	0.50
One East Asia (n=219)	20.5%	2.8 (1.9, 4.0)	<0.001
Both East Asia (n=316)	26.4%	3.9 (2.8, 5.2)	<0.001
<i>One South East Asia (n=167)</i>	22.8%	3.2 (2.1, 4.6)	<0.001
<i>Both South East Asia (n=116)</i>	27.6%	4.1 (2.7, 6.3)	<0.001
<i>One North East Asia (n=111)</i>	24.7%	2.7 (1.6, 4.3)	<0.001
<i>Both North East Asia (n=95)</i>	25.3%	3.6 (2.2, 5.9)	<0.001

Table S4: Country of birth of parents born in East Asia, by number of parents born in East Asia and length of residence in Australia

	One parent born in East Asia (n=219)				Both parents born in East Asia (n=316)					
	Mother		Father		Both parents*		In Aus <5 yrs		In Aus >5 yrs	
	N	%	N	%	N	%	N	%	N	%
Brunei	1	0.68	1	1.37	0	0.00	0	0.00	0	0.00
Burma	0	0.00	0	0.00	4	1.67	1	1.00	3	2.19
Cambodia	1	0.68	1	1.37	6	2.51	2	2.00	3	2.19
China	16	10.96	10	13.70	73	30.54	34	34.00	38	27.74
East Timor	0	0.00	1	1.37	0	0.00	0	0.00	0	0.00
Hong Kong	11	7.53	9	12.33	12	5.02	0	0.00	12	8.76
Indonesia	4	2.74	5	6.85	26	10.88	14	14.00	11	8.03
Japan	19	13.01	2	2.74	8	3.35	3	3.00	5	3.65
Korea	0	0.00	0	0.00	6	2.51	3	3.00	3	2.19
Laos	1	0.68	0	0.00	0	0.00	0	0.00	0	0.00
Malaysia	23	15.75	15	20.55	29	12.13	11	11.00	17	12.41
Myanmar	0	0.00	0	0.00	1	0.42	1	1.00	0	0.00
Philippines	20	13.70	6	8.22	30	12.55	17	17.00	13	9.49
Singapore	9	6.16	7	9.59	4	1.67	3	3.00	1	0.73
South Korea	4	2.74	2	2.74	5	2.09	4	4.00	1	0.73
Taiwan	4	2.74	0	0.00	3	1.26	0	0.00	3	2.19
Thailand	12	8.22	4	5.48	6	2.51	0	0.00	5	3.65
Vietnam	21	14.38	9	12.33	29	12.13	7	7.00	22	16.06
Total	146	100.00	73	100.00	239	100.00	100	100.00	137	100.00

*Among those with both parents born in the same country