

Which infants with eczema are at risk of food allergy? Results from a population-based cohort

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Clinical & Experimental Allergy

Summary

Background The relationship between early onset eczema and food allergy among infants has never been examined in a population-based sample using the gold standard for diagnosis, oral food challenge.

Objective We characterised the risk of challenge-proven food allergy among infants with eczema in the general population.

Methods One-year-old infants ($n = 4453$ meeting criteria for this analysis) were assessed for history of eczema, received a nurse-administered eczema examination and underwent skin prick testing to peanut, egg and sesame. Those with a detectable wheal to one of the test foods underwent an oral food challenge irrespective of wheal size. The risk of food allergy, stratified by eczema severity and age of onset, was estimated using multivariate logistic regression with population sampling weights.

Results One in five infants with eczema were allergic to peanut, egg white or sesame, compared to one in twenty-five infants without eczema (OR 6.2, 95% CI 4.9, 7.9, $P < 0.001$). The prevalence of peanut allergy was low in the absence of eczema (0.7% 95% CI 0.4, 1.1). Infants with eczema were 11.0 times more likely to develop peanut allergy (95% CI 6.6, 18.6) and 5.8 times more likely to develop egg allergy (95% CI 4.6, 7.4) by 12 months than infants without eczema. 50.8% of infants (95% CI 42.8, 58.9) with early eczema onset (< 3 months) who required doctor-prescribed topical corticosteroid treatment developed challenge-proven food allergy.

Conclusion and Clinical Relevance Eczema, across the clinical severity spectrum in infancy, is a strong risk factor for IgE-mediated food allergy. Infants with eczema were six times more likely to have egg allergy and 11 times more likely to have peanut allergy by 12 months than infants without eczema. Our data suggest that a heightened awareness of food allergy risk among healthcare practitioners treating infants with eczema, especially if early onset and severe, is warranted.

Keywords eczema, egg allergy, food allergy, infants, peanut allergy, population-based cohort, risk factors

Submitted 31 January 2014; revised 1 July 2014; accepted 18 July 2014

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Cite this as: P. E. Martin, J. K. Eckert, J. J. Koplin, A. J. Lowe, L. C. Gurrin, S. C. Dharmage, P. Vuillermin, M. L. K. Tang, A.-L. Ponsonby, M. Matheson, D. J. Hill, K. J. Allen and for the HealthNuts Study Investigators, *Clinical & Experimental Allergy*, 2015 (45) 255–264.

Introduction

In Australia, IgE-mediated food allergy affects up to one in ten infants by 12 months of age [1]. Food allergy is of concern for parents and clinicians alike due to the risk of severe reactions such as anaphylaxis, which are

increasing in prevalence, particularly in those < 5 years of age [2, 3]. Identification of infants most at risk of food allergy at a population-based level may enable targeted, early preventive interventions, with the aim of reversing the rise in food allergy prevalence.

Food allergy has been linked to eczema, a common paediatric condition with a spectrum of severity [4]. A strong association has been observed between severe

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eczema and challenge-confirmed food allergy in the clinical setting. Among infants attending a dermatology department, 80% of infants with severe eczema had probable food allergy based on high sensitisation levels to cow's milk, egg white or peanut [4]. However, there is no such evidence from population-based settings [5], and therefore whether these findings form a biased representation of the eczema population and subsequent risk of food allergy is unknown. In both the USA and the Australia, screening of infants with eczema for food sensitisation is not currently recommended in the absence of a reaction to a food upon consumption, or severe eczema that is refractory to treatment [6].

HealthNuts is a prospective population-based cohort study of allergic disease in early childhood with a view to an improved understanding of the evolution of the atopic march. One of its aims was to measure the prevalence and environmental risk factors for the development of IgE-mediated food allergy (confirmed by food challenge) to peanut, egg white or sesame at the age of 1 year [1, 7, 8]. We further aimed to characterise the role of eczema in the development of food allergy in the whole cohort according to the severity of eczema, age at eczema onset and socio-demographic and environmental factors using extensively gathered epidemiological data about eczema as well as an eczema examination conducted by SCORAD trained nurses. We also aimed to assess whether risk factors for food allergy differed between infants who had eczema and those who did not develop eczema in the first year of life.

Methods

Study design

The HealthNuts study is a population-based study of infants recruited at council-led immunization sessions in Melbourne, Australia. Recruitment took place between September 2007 and August 2011, and all infants aged between 11 and 15 months (inclusive) were eligible. Study methods have been described in detail previously [9]. Briefly, all participating infants were examined for eczema on the face, back and elbows and underwent a skin prick test (SPT) to four foods (egg white, peanut and sesame, plus cow milk or shell fish) as well as positive (histamine) and negative (saline) controls. Infants with any detectable SPT wheal reaction to food (minus the negative control) were invited for further follow-up in the HealthNuts allergy clinic where SPT was repeated, allergen-specific serum IgE was measured and oral food challenges to peanut, egg white or sesame were performed. Oral food challenges to cow's milk were not performed due to resource constraints. For a more detailed description on oral food challenge methods, see Koplin *et al*, [8]. All infants with a detectable wheal size were

offered an oral food challenge irrespective of wheal size. Parents completed a questionnaire, which collected information on the infant's eczema status, including medication and age of onset, as well as environmental and demographic factors. Families who declined participation were administered a brief questionnaire to aid in assessment of representativeness of the study sample [9].

Definition of food sensitisation and food allergy

Infants were categorised as food sensitised to egg white, peanut, cow's milk or sesame on the basis of the HealthNuts allergy clinic SPT or alternatively the serum food-specific IgE level (please see Summary of definitions for more details). Infants were further categorised as food allergic or food tolerant to egg white, peanut or sesame following an oral food challenge (using predetermined stopping criteria that only included objective signs of an immediate allergic reaction). A minority of infants were categorised as food allergic on the basis of a parent report of an immediate-type reaction to the food (vomiting, urticaria, angioedema and anaphylaxis) within the previous 1 month for egg white or 2 months for peanut and sesame [9].

Participants were classified as missing if they had an inconclusive oral food challenge and a repeat challenge was not undertaken or if they had evidence of food allergy on consumption (positive oral food challenge or recent parent-reported reaction) without evidence of food sensitisation on SPT or food-specific IgE.

Definition of eczema

An infant was considered to have eczema if they had a parent-reported history of eczema or if they had current eczema at time of recruitment on the face, back or elbow flexures [10], which were examined in the course of the community SPT.

A positive parent report of eczema was elicited from the question 'Has your child ever been diagnosed with eczema?' or from positive responses to both of 'Has child had itchy rash other than nappy rash?' and 'Was the itchy rash treated with topical steroid?'. Inclusion of infants with a history of an itchy rash treated with a topical steroid aimed to capture eczema cases that had not been diagnosed by a clinician at this early age, as previously described [11].

Infants were classified as 'missing' for eczema status if there were missing data for both current eczema and parent-reported history of eczema or if one was negative and the other missing. In the case of one missing measurement and one positive measurement, the infant was classified as having eczema.

Eczema severity was assessed for infants who met the eczema definition using four categories of treatment for

any rashes (from least to most severe): no moisturizers or topical steroids, moisturizers only, over-the-counter topical steroids and prescription-only topical steroids.

For infants with parent-reported diagnosed eczema, age at diagnosis was reported by parents on the questionnaire.

Summary of definitions

Food allergy or eczema category	Definition
Not food allergic and not food sensitised	SPT = 0 mm at time of recruitment to all foods tested in the community (egg white, peanut and sesame). No food challenge undertaken SPT < 2 mm at clinic attendance or serum food-specific IgE < 0.35 to all foods, and negative for any oral food challenges undertaken
Food sensitised and tolerant	Evidence of sensitisation to egg white, peanut &/or sesame: • SPT $\geq$ 2 mm at clinic and/or • Serum food-specific IgE $\geq$ 0.35 to egg white, peanut and sesame in clinic PLUS evidence for tolerance to the same food(s) upon consumption: • Negative to all oral food challenges undertaken
Food sensitised and allergic ('Food allergy')	Evidence of sensitisation to egg white, peanut &/or sesame: • SPT $\geq$ 2 mm at clinic, and/or • Serum food-specific IgE $\geq$ 0.35 to egg white, peanut and sesame in clinic PLUS evidence for allergic reactivity to the same food(s): • Positive oral food challenge, or • Unequivocal history of previous reaction within the last 1–2 months
No eczema	Negative for parent-reported diagnosed eczema and for itchy rash treated with topical steroids, and no current eczema (face, back or elbow flexures) at recruitment
Eczema	Parent-reported diagnosed eczema or itchy rash treated with topical steroids, or current eczema (face, back or elbow flexures, examined in course of SPT) at recruitment

Statistical analyses

The proportion of infants with food allergy (to any or each of egg white, peanut &/or sesame) was calculated and stratified by eczema status. The risk of food allergy, stratified by eczema, was then estimated using logistic regression with population sampling weights applied as previously described [10], to account for factors associated with a family's decision to participate in the study (family history of food allergy, asthma, eczema or allergic rhinitis, socioeconomic status, and whether the infant was tolerating peanut in their diet already). Food allergy risk was also calculated for eczema by severity and age at eczema onset.

Pearson's chi-square tests were used to identify socio-demographic and environmental factors that were provisionally associated with food allergy among infants with and without eczema. Associations were then modelled using a logistic regression comparing the odds of food allergy to the odds of being not allergic (including sensitised and non-sensitised infants), adjusting for potential confounding effects (see Table 3 for factors considered) and effect modification. Associated factors were tested for effect modification, with an interaction recorded if the interaction term fitted in the model improved the model significantly (likelihood ratio test, $P < 0.05$). Models were performed for two subgroups: infants with eczema, and infants without eczema. Finally, to assess whether factors were specific to the eczema or non-eczema subgroups, an interaction term was fitted between eczema and each factor in a logistic regression model inclusive of the entire participant group, and tested to see whether the interaction term improved the model significantly (likelihood ratio test, $P < 0.05$).

Ethics

Ethics approval for the HealthNuts study 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).

Results

Study participation

The participation rates for the initial recruitment phase and oral food challenge clinic phase are shown in Fig. 1. In total, 7134 infants were eligible for recruitment, and 5276 (74%) agreed to participate. A further 304 infants were excluded from the initial months of recruitment (pilot stage) due to differences in the questions regarding eczema status. Overall, 4453 infants met the definition criteria (positive or negative) for

eczema, food sensitisation and food allergy and were included in this analysis.

The risk of food allergy among infants with or without eczema

The proportion of infants with eczema who had food allergy was 21.5%, corresponding to an estimated risk of food allergy among the greater population of infants with eczema of 20.9% (Table 1). The risk of food allergy in infants with eczema was significantly higher than the infants without eczema (4.1%), corresponding to an odds ratio of 6.2 (95% CI 4.9, 7.9; $P < 0.001$).

The risk of specific food allergies to egg white, peanut or sesame was also higher among infants with eczema (OR 5.8, OR 11.0 and OR 41.4, respectively; Table 1). The risk of peanut allergy or sesame allergy was very low in the absence of eczema (0.7%, 95% CI 0.4, 1.1, and 0.04%, 95% CI 0.006, 0.31, respectively).

The risk of sensitisation to egg, peanut or sesame was also significantly higher among infants with eczema (OR 5.7, OR 8.3 and OR 7.9, respectively; Table 1), with the greatest relative difference was observed for peanut sensitisation (OR 8.3, 95% CI 6.2, 11.2). Infants with eczema were at increased risk of being sensitised to more than one of the foods tested (Table 1). The risk of sensitisation to cow's milk was also higher among infants with eczema (10.3%, 95% CI 8.5, 12.4) com-

pared to infants without eczema (1.6%, 95% CI 1.0, 2.3; OR 7.2, 95% CI 4.6, 11.4).

Clinical risk factors for food allergy among infants with eczema

The risk of food allergy among infants with eczema was greater among infants whose eczema was diagnosed at a younger age and among infants with more severe eczema. The food allergy risk for each age and severity category, estimated for the greater population of infants, is presented in Fig. 2. Infants with eczema diagnosed within the first 3 months after birth, and who required prescription topical corticosteroid treatments from a doctor, had the highest risk of food allergy (50.8%, 95% CI 42.8, 58.9).

Socio-demographic risk factors for food allergy among infants with or without eczema

Several socio-demographic and environmental factors were investigated as risk factors for food allergy among infants with and without eczema (Table 2).

After adjustment for other factors associated with food allergy in Table 2, male sex and having a father born in East Asia were associated with an increased risk of food allergy among infants with eczema (Table 3). Factors that reduced the risk of food allergy were pet

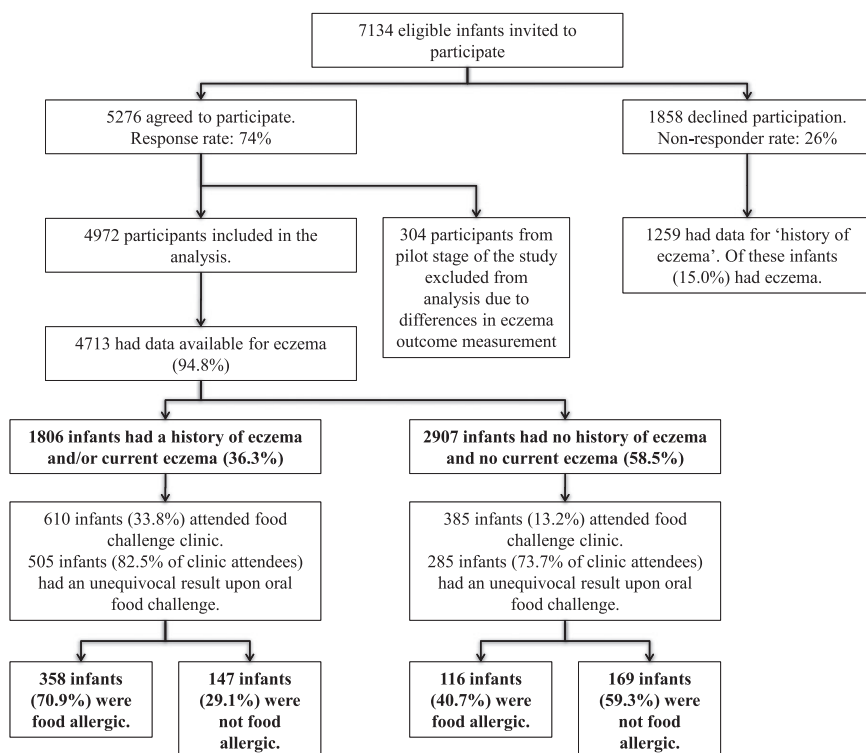


Fig. 1. Overview of study participation.

Table 1. Risk of food allergy and food sensitisation, stratified by eczema in the first year of life ($n = 4713$)

	No eczema		Eczema		OR* (95% CI)	P
	Proportion of HealthNuts Study participants	Population risk* % (95% CI)	Proportion of HealthNuts Study participants	Population risk* % (95% CI)		
Food allergy [†]	109/2705 (4.0%)	4.1% (3.4, 4.9)	375/1748 (21.5%)	20.9% (18.9, 22.9)	6.2 (4.9, 7.8)	<0.001
Food sensitisation, with tolerance [†]	55/2705 (2.0%)	2.0% (1.5, 2.6)	99/1748 (5.7%)	5.8% (4.8, 7.1)	3.1 (2.2, 4.4)	<0.001
Specific food sensitisations						
Egg white	139/2682 (5.2%)	5.1% (4.3, 6.0)	412/1713 (24.1%)	23.6% (21.5, 25.7)	5.7 (4.6, 7.0)	<0.001
Peanut	62/2739 (2.3%)	2.3% (1.8, 3.0)	294/1752 (16.8%)	16.5% (14.7, 18.4)	8.3 (6.2, 11.2)	<0.001
Sesame	30/2732 (1.1%)	1.0% (0.7, 1.5)	141/1785 (7.9%)	7.7% (6.5, 9.1)	7.9 (5.2, 12.2)	<0.001
Number of food sensitisation [†]						
One	197/2745 (7.2%)	7.1% (6.1, 8.2)	338/1791 (18.9%)	19.1% (17.2, 21.0)	3.1 (2.5, 3.8)	<0.001
Two	29/2745 (1.1%)	1.1% (0.8, 1.6)	151/1791 (8.4%)	8.2% (7.0, 9.7)	8.1 (5.4, 12.3)	<0.001
Three	2/2745 (0.07%)	0.04% (0.005, 0.26)	43/1791 (2.4%)	2.3% (1.7, 3.2)	66.2 (9.6, 508.2)	<0.001
Specific food allergies						
Egg white allergy	101/2720 (3.7%)	3.7% (3.0, 4.5)	327/1735 (18.8%)	18.3% (16.4, 20.3)	5.8 (4.6, 7.4)	<0.001
Peanut allergy	17/2762 (0.6%)	0.7% (0.4, 1.1)	126/1783 (7.1%)	6.8% (5.7, 8.2)	11.0 (6.6, 18.6)	<0.001
Sesame allergy	1/2741 (0.04%)	0.04% (0.006, 0.31)	32/1815 (1.8%)	1.8% (1.2, 2.6)	41.4 (5.6, 304.6)	<0.001
Number of food allergies [†]						
One	97/2667 (3.6%)	3.7% (3.0, 4.5)	253/1675 (15.1%)	14.8% (13.1, 16.7)	4.6 (3.6, 5.9)	<0.001
Two	10/2667 (0.4%)	0.4% (0.2, 0.7)	76/1675 (4.5%)	4.3% (3.4, 5.5)	11.4 (5.8, 22.3)	<0.001
Three	0 (0%)	—	15/1675 (0.9%)	0.8% (0.5, 1.4)	—	—

*Weighted for factors associated with participation in the HealthNuts study: family history of food allergy, family history of allergy (asthma, eczema or allergic rhinitis), family size, socio-economic status and whether the infant was tolerating peanut in their diet.

[†]Number of food sensitisations and allergies only includes egg white, peanut and sesame.

dog ownership and pre-term birth (born at or less than 36 weeks gestation). Among infants with eczema, cat ownership was found to be a risk factor or protective factor depending on the child's ethnicity.

Infants without eczema had an increased risk of food allergy if their mother had eczema (Table 3) although parental history of other allergic diseases was not associated (data not shown). The risk of food allergy among those without eczema was also increased if the infant had no or few siblings.

During testing for effect modification between factors on the risk of food allergy, an interaction was found between cat ownership and East Asian ethnicity. Among infants with eczema whose father was born in East Asia ($n = 176$), there was an increased risk of food allergy if their family owned a cat (OR 9.4, 95% CI 0.96, 92.0, $P = 0.054$). Among the rest of the infants with eczema ($n = 1558$), cat ownership conveyed a protective effect against food allergy (OR 0.6, 95% CI 0.4, 0.9, P for interaction = 0.0008).

On face value, the pattern of risk factors for food allergy appeared to differ between infants with eczema and infants without eczema. However, on formal tests of interaction, there was no evidence that the relationship between any of the variables investigated and food allergy was modified by eczema status.

Discussion

Our study is the largest of its kind to examine the risk of confirmed food allergy in a general population sample, encompassing the entire spectrum of eczema severity. We found that infants with eczema are approximately five times more likely to develop IgE-mediated food allergy than infants without eczema. One in five infants with eczema had confirmed food allergy to egg white, peanut or sesame by 12 months of age, compared to only one in 25 infants without eczema. Peanut allergy and sesame allergy were rare in the absence of eczema, as were allergies or sensitisation to multiple foods. We also found that the risk of food allergy was greatest among those with early onset and severe eczema, with up to 50% of this group developing challenge-proven food allergy by 12 months of age.

We additionally considered demographic and environmental associations to help identify infants with eczema at further increased risk of food allergy. Male sex and East Asian ethnicity conveyed an increased risk of food allergy among infants with eczema, while infants who were exposed to a pet dog or born pre-term (less than 36 weeks gestation) had a lower risk of food allergy. However, our formal assessment of

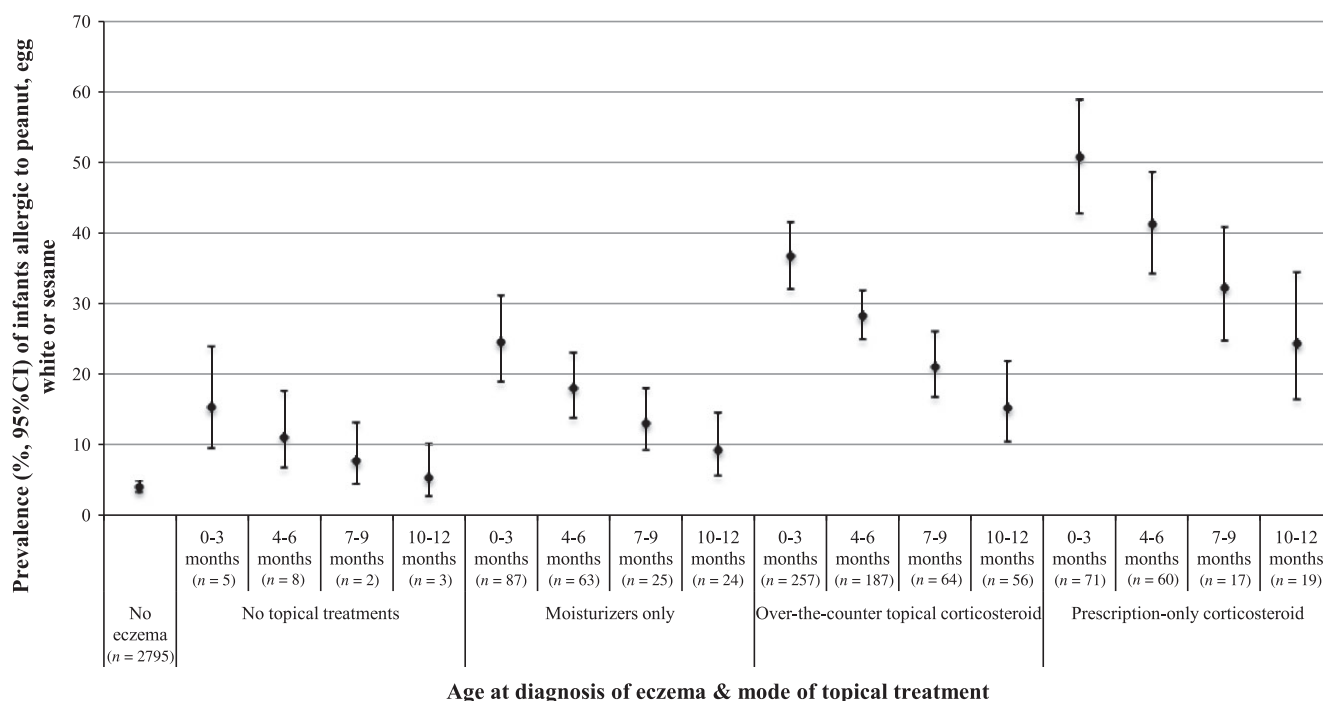


Fig. 2. The risk of food allergy among infants with eczema, stratified by age at diagnosis of eczema and mode of topical treatment for eczema. Food allergy to peanut, egg white or sesame was assessed using oral food challenges. Risk estimates for food allergy and 95% confidence intervals were predicted using a logistic regression model with mode of topical treatment (four categories) and age at diagnosis of eczema (four categories) modelled as linear variables.

interaction revealed that these factors had a similar magnitude of effect for food allergy regardless of whether the infant had eczema or not. Larger studies would be required to further investigate whether there is indeed a differential risk for food allergy between these two groups. We did not seek to establish causation relationships in our current analysis, and reverse causality may play a role in our findings. For example, a family with relatively few cases of atopy, particularly animal dander sensitisation, may be more likely to own a pet, but less likely to have a child with food allergy related to the absence of family history of atopy.

Strengths of our analysis include a sensitive measure of eczema applied to the whole study cohort, including ascertainment of history of previously doctor-diagnosed cases as well as nurse observed assessment in all infants at age 12 months. Additionally, food allergy was assessed by standardised oral food challenges for any infants with a detectable wheal size at screening. Validity of the population representativeness of the HealthNuts study has been previously reported [9] and was strengthened by the use of a non-participant questionnaire which enabled prevalence figures to be reweighted to account for allergic bias to participate.

Limitations of our study include the retrospective collection of exposure data, although questionnaire

data at age 12 months were obtained prior to knowledge about food sensitisation and food allergy by participant's parents and therefore bias should be non-differential by food allergy status. Another limitation is that oral food challenges were not placebo controlled and double-blinded; however, PRACTALL guidelines have outlined that open food challenges for infants due to their unlikelihood to have false-positive results related to subjective symptoms [12]. Due to resource constraints, we were unable to conduct oral food challenges for foods other than peanut, sesame and egg white; hence, our limited sensitisation and allergy data remain a source of potential misclassification. Some infants that are allergic to other common allergens, such as treenuts, may have been missed, leading to potential underestimation or overestimation of the association effect sizes. A proportion of infants that were allergic to foods that were not tested in this study may have been captured by cases of egg, peanut or sesame allergy. Within the HealthNuts study, all cases of milk sensitisation ($n = 60$) also had sensitisations to egg white, peanut or sesame (data not shown), indicating some overlap between common allergens.

Our findings confirm and extend previous studies suggesting a strong association between eczema in infancy and the development of food allergy [4, 13]. We are limited in comparing our study to these

Table 2. Socio-demographic characteristics of infants with and without eczema ($n = 4713^*$), stratified by food allergy status

		No Eczema			Eczema		
		No food allergy	Food allergy	P (from χ^2 test)	No food allergy	Food allergy	P (from χ^2 test)
Gender	Male	1225 (96%)	51 (4.0%)	0.887	745 (76.25%)	232 (23.75%)	0.010
	Female	1355 (95.9%)	58 (4.1%)		621 (81.39%)	142 (18.61%)	
Mode of delivery	Vaginal	1744 (95.82%)	76 (4.18%)	0.638	883 (77.52%)	256 (22.48%)	0.17
	Caesarean	837 (96.21%)	33 (3.79%)		483 (80.37%)	118 (19.63%)	
Preterm birth (≤ 36 weeks)	No	2341 (95.82%)	101 (4.18%)	0.378	1217 (78.06%)	342 (21.94%)	0.012
	Yes	144 (97.3%)	4 (2.7%)		97 (88.18%)	13 (11.82%)	
Low birth weight (≤ 2500 g)	No	2410 (95.9%)	103 (4.1%)	0.159	1274 (78.11%)	357 (21.89%)	0.043
	Yes	124 (98.41%)	2 (1.59%)		85 (86.73%)	13 (13.27%)	
Number of siblings	None	1264 (94.82%)	69 (5.18%)	0.007	654 (76.94%)	196 (23.06%)	0.24
	1	843 (96.56%)	30 (3.44%)		480 (80.0%)	120 (20.0%)	
	2	350 (98.31%)	6 (1.69%)		166 (77.57%)	48 (22.43%)	
	3 or more	119 (98.35%)	2 (1.65%)		55 (85.94%)	9 (14.06%)	
Socio-economic status (SEIFA quintiles*)	1 (most disadvantaged)	566 (97.08%)	17 (2.92%)	0.524	257 (82.11%)	56 (17.89%)	0.291
	2	513 (95.35%)	25 (4.65%)		282 (76.42%)	87 (23.58%)	
	3	554 (96.18%)	22 (3.82%)		298 (80.11%)	74 (19.89%)	
	4	496 (95.75%)	22 (4.25%)		283 (78.18%)	79 (21.82%)	
	5 (most advantaged)	459 (95.23%)	23 (4.77%)		250 (76.22%)	78 (23.78%)	
History of wheeze	No	1968 (95.81%)	86 (4.19%)	0.585	954 (78.20%)	266 (21.8%)	0.331
	Yes	376 (96.41%)	14 (3.59%)		263 (80.67%)	63 (19.33%)	
Maternal eczema	No	2318 (96.34%)	88 (3.66%)	0.005	1106 (79.28%)	289 (20.72%)	0.136
	Yes	278 (92.98%)	21 (7.02%)		267 (75.64%)	86 (24.36%)	
Paternal eczema	No	2446 (96.19%)	97 (3.81%)	0.024	1234 (78.5%)	338 (21.5%)	0.883
	Yes	150 (92.59%)	12 (7.41%)		139 (78.98%)	37 (21.02%)	
Sibling eczema	No	2300 (95.67%)	104 (4.33%)	0.027	1130 (78.97%)	301 (21.03%)	0.365
	Yes	296 (98.34%)	5 (1.66%)		243 (76.66%)	74 (23.34%)	
	Yes	106 (96.81%)	7 (6.19%)		73 (75.26%)	24 (24.74%)	
Parental latex allergy	No	2533 (96.17%)	101 (3.83%)	0.002	1319 (78.65%)	358 (21.35%)	0.602
	Yes	63 (88.73%)	8 (11.27%)		54 (76.06%)	17 (23.94%)	
Mother took iron during pregnancy	No	348 (93.8%)	23 (6.2%)	0.026	166 (78.3%)	46 (21.7%)	0.972
	Yes	2117 (96.27%)	82 (3.73%)		1144 (78.41%)	315 (21.59%)	
Maternal tobacco smoking (current)	No	2405 (95.97%)	101 (4.03%)	0.885	1278 (78.02%)	360 (21.98%)	0.028
	Yes	152 (96.2%)	6 (3.8%)		79 (87.78%)	11 (12.22%)	
Maternal cigarette smoking (past)	No	1709 (95.96%)	72 (4.04%)	0.711	885 (75.84%)	282 (24.16%)	<0.001
	Yes	873 (96.25%)	34 (3.75%)		475 (84.22%)	89 (15.78%)	
Maternal cigarette smoking during pregnancy	No	2450 (96.0%)	102 (4.0%)	0.568	1294 (77.95%)	366 (22.05%)	0.004
	Yes	129 (96.99%)	4 (3.01%)		69 (92.0%)	6 (8.0%)	
Paternal cigarette smoking (current)	No	2151 (96.11%)	87 (3.89%)	0.437	1171 (78.70%)	317 (21.30%)	0.675
	Yes	406 (95.31%)	20 (4.69%)		186 (77.5%)	54 (22.5%)	
Paternal cigarette smoking (past)	No	1537 (95.94%)	65 (4.06%)	0.691	843 (77.98%)	238 (22.02%)	0.444
	Yes	1001 (96.25%)	39 (3.75%)		502 (79.56%)	129 (20.44%)	
Ever migrated to Australia	No	1495 (96.58%)	53 (3.42%)	0.426	830 (83.33%)	166 (16.67%)	<0.001
	Yes	407 (95.76%)	18 (4.24%)		209 (66.99%)	103 (33.01%)	
Parental ethnicity	Australia	1570 (96.62%)	55 (3.38%)	0.053	869 (83.32%)	174 (16.68%)	<0.001
	East Asia/Far East	92 (90.2%)	10 (9.8%)		83 (60.14%)	55 (39.86%)	
	UK/Britain	29 (93.55%)	2 (6.45%)		13 (68.42%)	6 (31.58%)	
	South Asia	24 (100%)	0		4 (80.0%)	1 (20.0%)	
	Europe	26 (100%)	0		11 (78.57%)	3 (21.43%)	
	Africa	30 (96.77%)	1 (3.23%)		14 (77.78%)	4 (22.22%)	
	North America	3 (100%)	0		0	0	

Table 2 (continued)

		No Eczema			Eczema		
		No food allergy	Food allergy	<i>P</i> (from χ^2 test)	No food allergy	Food allergy	<i>P</i> (from χ^2 test)
Mother born in East Asia (only)	South America	5 (100%)	0		1 (50%)	1 (50%)	
	Middle East	29 (100%)	0		17 (85.0%)	3 (15.0%)	
	Oceania	29 (100%)	0		10 (66.67%)	5 (33.33%)	
Father born in East Asia (only)	No	2512 (96.02%)	104 (3.98%)	0.438	1320 (78.95%)	352 (21.05%)	0.056
	Yes	84 (94.38%)	5 (5.62%)		53 (69.74%)	23 (30.26%)	
Pets at home (any)	No	2564 (95.92%)	109 (4.08%)	0.244	1351 (79.01%)	359 (20.99%)	0.002
	Yes	32 (100%)	0		22 (57.89%)	16 (42.11%)	
Pet cat	No	1373 (95.81%)	60 (4.19%)	0.62	732 (74.47%)	251 (25.53%)	<0.001
	Yes	1187 (96.19%)	47 (3.81%)		621 (84.72%)	112 (15.28%)	
Pet dog	No cat	2134 (95.87%)	92 (4.13%)	0.556	1122 (77.17%)	332 (22.83%)	0.002
	Cat	462 (96.45%)	17 (3.55%)		251 (85.37%)	43 (14.63%)	
Pet dog	No dog	1748 (95.73%)	78 (4.27%)	0.356	934 (75.87%)	297 (24.13%)	<0.001
	Dog	848 (96.47%)	31 (3.53%)		439 (84.91%)	78 (15.09%)	

*Total number of infants available for each comparison varies due to missing data for each socio-demographic characteristic.

Bold values: $P \leq 0.05$.

Table 3. Multilogistic regression to assess factors associated with the development of food allergy among infants without and with eczema ($n = 4713$)

	Among infants <i>without</i> eczema ($n = 2795$)			Among infants <i>with</i> eczema ($n = 1903$)			<i>P</i> for difference between infants with and without eczema [‡]
	Unadjusted OR	Adjusted OR [†]	<i>P</i>	Unadjusted OR	Adjusted OR [†]	<i>P</i>	
Demographic factors							
Male sex	1.0 (0.7, 1.4)	0.9 (0.6, 1.3)	0.58	1.4 (1.1, 1.7)*	1.4 (1.1, 1.8)	0.010	0.14
Pre-term birth	0.6 (0.2, 1.8)	0.7 (0.3, 2.1)	0.56	0.5 (0.3, 0.9)*	0.5 (0.2, 0.9)	0.014	0.64
Number of siblings	0.6 (0.5, 0.8)***	0.6 (0.4, 0.8)	0.001	0.9 (0.8, 1.0)	0.9 (0.8, 1.0)	0.17	0.13
Maternal eczema	2.0 (1.2, 3.3)**	1.7 (1.0, 2.9)	0.07	1.2 (0.9, 1.6)	1.1 (0.8, 1.6)	0.40	0.11
Paternal eczema	2.0 (1.1, 3.8)*	1.6 (0.8, 3.4)	0.18	1.0 (0.7, 1.4)	1.0 (0.6, 1.5)	0.94	0.06
Parental latex allergy	3.2 (1.5, 6.8)**	3.8 (1.6, 8.5)	0.002	1.2 (0.7, 2.0)	1.3 (0.7, 2.3)	0.47	0.046
Mother born in East Asia	2.2 (1.2, 3.8)**	2.2 (0.9, 4.9)	0.07	2.4 (1.8, 3.2)***	1.2 (0.7, 1.9)	0.53	0.79
Father born in East Asia	2.0 (1.0, 4.0)*	1.0 (0.3, 2.7)	0.96	2.8 (2.0, 3.9)***	2.2 (1.4, 3.7)	0.001	0.38
Environmental factors							
Mother smoked in pregnancy	0.7 (0.3, 2.1)	1.0 (0.4, 2.9)	0.98	0.3 (0.1, 0.7)**	0.5 (0.2, 1.1)	0.09	0.21
Pet dog	0.8 (0.5, 1.3)	0.9 (0.6, 1.5)	0.76	0.6 (0.4, 0.7)***	0.7 (0.5, 0.9)	0.006	0.14
Pet cat	0.9 (0.5, 1.4)	0.9 (0.5, 1.6)	0.65	0.6 (0.4, 0.8)**	0.6 (0.4, 0.9)	0.017	0.24
Mother took iron supplements during pregnancy	0.6 (0.4, 0.9)*	0.5 (0.3, 0.9)	0.011	1.0 (0.7, 1.4)	1.0 (0.7, 1.5)	0.99	0.09

Reference group for food allergy outcome are all non-allergic infants (sensitised and tolerant, and non-sensitised).

* $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$.

[†]Adjusted for all other factors in the table that had an unadjusted OR with $P < 0.05$ for either infants with eczema or infants without eczema.

[‡]Assessed using likelihood ratio tests, comparing logistic regression models of food allergy risk, with and without an interaction term being fitted between eczema and the other factor being considered.

Bold values: $P \leq 0.05$.

studies as they did not have challenge-proven outcomes and all were clinic-based, which in both cases may have led to bias of association. Current guidelines for food allergy diagnosis from an NIAID-sponsored panel do not recommend screening infants with eczema unless there is clinical evidence of an IgE-mediated food reaction, or the eczema is refractory to treatment [6].

Our data suggest that a heightened awareness of food allergy risk among healthcare practitioners treating infants with early onset moderate to severe infantile eczema is warranted. This subgroup of infants could be targeted for either early detection or early application of prevention strategies for food allergy that may become available in the future.

Our findings with regard to the role of preterm birth in the development of food allergy are intriguing and support previous studies assessing the role of prematurity and allergic sensitisation [14, 15]. Although both these studies were performed on very premature born children (weight < 1500 g) compared to our group (< 36 weeks, mean birth weight 2462.4 g, with 25 children < 1500 g), we think some of the same environmental and developmental conditions may apply. Siltanen et al. hypothesised that the protective association found may have been due to increased infections, specifically respiratory infections in preterm born infants in their study suggesting support for the hygiene hypothesis in protection from atopy. Others have argued that differences in gut flora of preterm vs. term babies may influence the development of allergic sensitisation [16, 17] or even differential epigenetic priming due to preterm birth [18]. Although no study has directly investigated the role of epigenetics on the development of food allergy or sensitisation as yet [19], previous studies have demonstrated that environmental exposures such as smoking influence epigenetic priming and potentially disease development [20, 21]. Alternatively the absence of as yet unidentified factors transferred transplacentally in the 3rd trimester may play a role.

The association between eczema and food allergy may be the result of an antecedent factor common to both conditions, or may be explained by a causal link. The magnitudes of association between having eczema and being sensitised to egg white or peanut, and having eczema and being allergic to egg or peanut, were very similar. Our findings provide epidemiological support for the dual-allergen-exposure hypothesis [22] which states that increased cutaneous exposure to food allergens in infants with weakened skin barrier function due to, for example early onset or severe eczema, have an increased risk of food sensitisation. The dual-allergen-exposure hypothesis is supported by our previous finding: that filaggrin gene (FLG) mutations that are associated with an impairment of skin barrier function and lead to an increased risk of food sensitisation among infants with eczema [23]. However, a putative role for FLG mutations in eczema and food allergy is not consistent between studies. A recent study among breastfed infants found that the risk of food sensitisation was more related to eczema severity, and independent of FLG carriage [24]. FLG mutations have been associated with eczema sever-

ity and an increased risk of peanut allergy in separate studies [25, 26]. In our analysis, the prevalence of peanut allergy was low in the absence of eczema. We attempted to identify a second factor that may increase the risk of food allergy above that of eczema but were unable to determine any specific to this subgroup.

In conclusion, early onset eczema in infancy, particularly moderately severe, is a strong risk factor for IgE-mediated food allergy. Infants with early onset severe eczema could be targeted for advice about introduction of food, and future interventions aimed at reducing the prevalence of food allergy.

Acknowledgements

We thank the children and parents who participated in the HealthNuts Study as well as the staff of Melbourne's Local Government Areas for access to community Immunization Clinics. We thank the HealthNuts safety committee: Associate Professor Noel Cranswick (Australian Paediatric Pharmacology Research Unit, Murdoch Childrens Research Institute), Dr Joanne Smart (Department of Allergy and Immunology, Royal Children's Hospital, Melbourne, Australia) and Professor Jo Douglass (Director, Department of Allergy and Immunology, Royal Melbourne Hospital, Melbourne, Australia). We thank ALK Abello, S.A. Madrid, España for the provision of allergen for SPT.

Funding

This work is funded by NHMRC Australia (APP491233), the Ilhan Food Allergy Foundation, AnaphylaxisStop, ALK Abello, S.A. Madrid, España, the Charles and Sylvia Viertel Medical Research Fellowship awarded to Katie Allen and the Victorian Government's Operational Infrastructure Support Program.

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