

The Prevalence of Food Sensitization Appears Not to Have Changed between 2 Melbourne Cohorts of High-Risk Infants Recruited 15 Years Apart



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What is already known about this topic? Recent reports suggest that the prevalence of food sensitization in the general population of older children has not changed over the last 2 decades, which is surprising considering the apparent increase in food allergy reported from multiple sources.

What does this article add to our knowledge? This article suggests that the prevalence of food sensitization has remained stable between 1990-1994 and 2007-2011 among infants at high risk of food allergy with a family history of allergic disease, even though anaphylaxis hospital admission rates have increased markedly over this same period.

How does this study impact current management guidelines? These findings suggest that because the prevalence of food sensitization has not changed, the increase in food allergy could be due to an increase in the proportion of high-risk infants within the total population, an increase in food allergy in the low-risk group, or changes in the relationship between food sensitization and food allergy. An alternative explanation is that food allergy may not be on the rise and any apparent increase is due to increased awareness, informal self-reported diagnosis, formal diagnosis by health professionals, or increased number and/or severity of reactions, particularly anaphylaxis.

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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 research support from the National Health and medical Research Council Australia and 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. M. Wake has received research support from the Australian National Health & Medical Research Council, NZ Ministry of Business, Innovation & Employment, and Cure Kids/A Better Start; has received a fellowship from Australian National Health & Medical Research Council; has received sitting fees from the Australian Government; and has received support to present at a symposium from Sandoz. M. J. Abramson has received research support from Pfizer and Boehringer Ingelheim; and has received travel support from Sanofi. The rest of the authors declare that they have no relevant conflicts of interest.

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Abbreviations used

CI- Confidence interval

MACS- Melbourne Atopy Cohort Study

PPV- Positive predictive value

SPT- Skin prick test

BACKGROUND: Although food allergy has probably risen over recent decades, recent reports suggest that the prevalence of food sensitization in the general population has not changed.

However, this has not been analyzed in infants at high risk of food allergy.

OBJECTIVE: The objective of this study was to compare the prevalence of food sensitization in high-risk infants from 2 cohorts recruited 15 years apart in the same region.

METHODS: This study includes 620 high-risk infants with a family history of allergy (Melbourne Atopy Cohort Study [MACS]) born 1990-1994, and a subgroup of high-risk infants from the population-based HealthNuts study ($n = 3,661/5,276$), born 2006-2010. Both studies undertook skin prick tests (SPT) to peanut, egg, and milk at age 12 months. A logistic regression model generated adjusted prevalences to account for differences in sampling frame. $SPT \geq 95\%$ positive predictive values (PPVs) for food allergy were used as proxies for food allergy.

RESULTS: The adjusted prevalence of sensitization in MACS was similar to the observed prevalence of sensitization in the high-risk subgroup of HealthNuts: 7.9% (95% confidence interval 6.8-8.9) and 7.9% (7.0-8.8) respectively for peanut, 15.0% (13.4-16.6) and 14.5% (13.4-15.7) respectively for egg, and 2.4% (1.6-3.1) and 2.6% (2.0-3.4) respectively for cow's milk. The prevalence of $SPT \geq 95\%$ PPVs was similar between the 2 studies.

CONCLUSIONS: The prevalence of food sensitization among high-risk infants has remained stable in Australia since the 1990s, despite the reported increase in food-related anaphylaxis in the same period. This discrepancy could be due to increased food allergy in the low-risk population, increased conversion of food sensitization to allergy, or increased number of high-risk infants. Alternatively, increased awareness or severity of reactions may have led to an apparent increase in food allergy. © 2017 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2018;6:440-8)

Key words: Cow's milk allergy; Egg allergy; Food allergy; Food sensitization; Peanut allergy; Time trends

It has been suggested that the prevalence of food allergy has risen over the last 2 decades, representing a "second wave" of the allergy epidemic.¹ Data to support this increased prevalence come from published reports of increased hospital admissions for anaphylaxis, auto-injector adrenaline prescriptions, referrals for allergy services, and reports of doctor-diagnosed food allergies.²⁻¹⁰ Repeated cross-sectional studies are needed to establish an increase in prevalence; there is, however, only one such food allergy prevalence study in the same region using oral food challenge-proven outcomes. In that study, the prevalence of food allergy in 0- to 2-year olds from Chongqing, China, increased from 3.5% in 1999 ($n = 314$) to 7.7% in 2009 ($n = 401$, $P = .017$).¹¹

A related measure is food sensitization, an immunological biomarker of a predisposition to food allergy. Food sensitization is a necessary, but not sufficient condition for food allergy: only a proportion of those with detectable food-specific IgE will develop clinically provable food allergy, with the remainder being sensitized yet able to tolerate the food. Nevertheless, the prevalence of food sensitization remains an indicator of the prevalence of food allergy.

In the Chinese study, the prevalence of food sensitization rose from 9.9% in 1999 to 18.0% in 2009.¹¹ In contrast, 2 recent reports from substantially larger repeated cross-sectional studies have demonstrated that the prevalence of food sensitization has remained stable over a similar time period. In the United States, the prevalence of sensitization to peanut, egg, and milk among 6- to 19-year olds remained stable between 1988-1994 and 2005-2006, although there was a trend towards increased high-level peanut sensitization, but only among non-Hispanic black children, whereas the prevalence of shrimp sensitization decreased.¹² Egg and milk allergy are common food allergies in infancy that frequently resolve in early childhood, so the older children in these cohorts may not be the optimal age to assess time trends in prevalence of egg and milk sensitization. In the UK, peanut sensitization in 2 birth cohorts recruited 12 years apart (1989 and 2001-2002) was nearly identical at age 1 year. Although peanut sensitization was higher in the more recent cohort between ages 2 and 10 years, this difference was not statistically significant. The prevalence of peanut allergy at age 10 years was also higher in the more recent cohort 1.5% versus 0.58% although this difference did not quite reach statistical significance ($P = .09$).¹³

Changes in the prevalence of food sensitization in Australia, which has the highest reported prevalence of challenge-confirmed food allergy internationally, have not previously been investigated using data collected from repeated cross-sectional studies.¹⁴ Moreover, the above studies did not assess changes in the prevalence of food sensitization stratified for risk determined by the family history of allergic disease. Here we investigated the prevalence of food sensitization among high-risk infants with a family history of allergic disease between 2 cohorts of infants recruited in Melbourne, Australia, 15 years apart.

METHODS

Data used in the present analysis include 620 infants with a family history of allergy from the Melbourne Atopy Cohort Study (MACS) recruited between 1990 and 1994, and 5,276 infants from the population-based HealthNuts study, born in 2006-2010 and recruited at age 12 months (2007-2011). Both studies undertook skin prick tests (SPT) to common food allergens (egg, peanut, and milk) at 12 months of age using the same lancet device.^{15,16} Sensitization was defined at $SPT \geq 2$ mm and the 95% positive predictive value (PPV) for clinical food allergy was defined at $SPT \geq 8$ mm for peanut and milk and $SPT \geq 4$ mm for egg.¹⁷

Melbourne Atopy Cohort Study

MACS is a high-risk longitudinal birth cohort of 620 infants and their families who were recruited between 1990 and 1994. Expectant mothers were approached during routine antenatal care and invited to enrol in the study if the unborn child had a parent or older sibling with a history of allergic disease (asthma, eczema, allergic rhinitis, or food allergy). The MACS infants were followed up 18 times in the first 2 years of life by use of a nurse-administered

telephone survey. Clinical visits for SPT were performed at 6, 12, and 24 months; only the SPT conducted at 12 months of age was used in this analysis. The SPT panel consisted of 3 foods: peanut, egg white, and cow's milk, and 3 aeroallergens: house dust mite, rye grass, and cat dander (Bayer, Spokane, Wash; ALK-Abello, Round Rock, Tex; Hollister-Stier, Spokane, Wash). SPT were administered on the infants' back using a lancet and read after 15 to 20 minutes. Ethics approval was obtained from the Mercy Maternity Hospital's Human Research Ethics Committee.^{15,18}

HealthNuts

The HealthNuts study is a population-based longitudinal food allergy study consisting of 5,276 12-month-old infants who were recruited from council-run immunization centers during 2007-2011. Infants underwent SPT at 12 months of age (ALK-Abello, Madrid, Spain) to 4 common food allergens (peanut, egg white, sesame, and either cow's milk or shrimp). SPT were administered on the infants' back using a single-tine lancet (Stallergenes, Antony, France). Parents completed a questionnaire while the SPT was undertaken, but before it was read, which included information on the family history of allergy. HealthNuts infants were similar to the general population of infant births in Victoria with the exception that their mothers were slightly older.^{16,19} Ethics approval was obtained for the HealthNuts study from the Victorian State Government Office for Children (reference no. CDF/07/492), the Victorian State Government Department of Human Services (reference no.10/07), and the Royal Children's Hospital Human Research Ethics Committee (reference no. 27047).

Statistical methods

High-risk infants were defined as those with 1 or more family members with a history of allergic disease (eczema, asthma, food allergy, or hay fever). Because of the eligibility criteria, all MACS participants were high-risk infants, whereas the HealthNuts study contained both low- and high-risk infants. Baseline characteristics of both studies were compared and assessed using the χ^2 test for binary variables, for both the whole cohorts and the high-risk subgroup of HealthNuts compared with the whole MACS cohort that was high-risk by definition.

A multivariable logistic regression model was used to generate predicted probabilities of sensitization given covariates. The logistic regression model was fitted for each outcome of sensitization, including as covariates in the model the study indicator (HealthNuts or MACS) and demographic factors (maternal or paternal history of individual allergy, child's sex, and parent's country of birth) that were associated with the outcome on univariate analysis. As data from both studies were included in the same model, interactions were fitted between each covariate and the study indicator that allowed for the magnitude of association between covariate and outcome to vary between the studies. This was equivalent to fitting separate models to data from each cohort, but computationally convenient for cross-cohort prediction. Interactions were retained in the final model if the *P* value from the likelihood ratio test was less than .10. The adjusted prevalence of sensitization for the MACS covariate distribution given the HealthNuts association model was obtained by averaging covariate-specific predictions in the MACS cohort using the final model fitted to the whole HealthNuts data over the distribution of included covariates in the MACS cohort. Similarly, the adjusted prevalence given the covariate distribution in the HealthNuts cohort was calculated by averaging covariate-specific predictions from the MACS association model firstly for the whole

HealthNuts population, and then separately for the low- and high-risk subgroups.

This procedure effectively standardized the prevalence estimates from a regression model in 1 cohort (thus capturing the magnitude of exposure-outcome associations in that cohort) to the covariate distribution of the other cohort. This allowed us to compare average prevalence between cohorts where the only difference was in the risk factor distribution.²⁰ Model fits, predictions, and standard errors were generated using the margins command in Stata Version 14.0 (College Station, Tex). Food challenge data were not available in the MACS study; therefore, we additionally compared SPT 95% PPVs as a proxy for food allergy, using a threshold of ≥ 4 mm for egg and ≥ 8 mm for peanut and milk.¹⁷ The regression models used in the standardization procedure are included in Table E1 in this article's Online Repository at www.jaci-inpractice.org. A decision was made *a priori* to only include the parental history factors in the standardization procedure because that is what the differences in sampling frame were based on (MACS eligibility criteria) and presumably the difference between the 2 cohorts, other than time. Although eczema is a strong risk factor for food sensitization and potentially on the causal pathway, it is a post-birth marker and will not have influenced participation in the MACS study. However, we additionally conducted a sensitivity analysis including eczema as a covariate in the regression model.

RESULTS

Participation in MACS and HealthNuts has been described in detail previously.^{15,16} As expected, a higher proportion of maternal and paternal history of allergy was observed in the MACS high-risk cohort compared with the HealthNuts population-based cohort (see Table E2 in this article's Online Repository at www.jaci-inpractice.org). All MACS participants were classified as high-risk with 1 or more first degree family members having a history of allergic disease, whereas 69.4% (3,661/5,276) of HealthNuts participants were classified as high-risk. The demographic characteristics of high-risk HealthNuts participants and MACS participants are presented in Table I. The proportion of family members with a history of allergic disease was higher among the MACS participants even when compared with the corresponding proportion in the high-risk HealthNuts participants. There were more Asian parents in HealthNuts compared with MACS, which is likely to reflect changes in the population composition of Melbourne over this period of time.

The observed prevalence of food sensitization was lower in the whole and high-risk subgroup of the HealthNuts cohort compared with MACS, which was not surprising given the differences in sampling frame (Table II). However, after standardization of the MACS cohort to the HealthNuts cohort (Figure 1), the adjusted prevalence of peanut sensitization in MACS was very similar to the observed prevalence in high-risk HealthNuts, 7.9% (95% confidence interval [CI] 6.8-8.9) and 7.9% (95% CI 7.0-8.8), respectively. A similar pattern was observed for both egg and milk sensitization. The adjusted prevalence of egg sensitization in MACS was very similar to the observed prevalence of egg sensitization in high-risk HealthNuts, 15.0% (95% CI 13.4-16.6) and 14.5% (95% CI 13.4-15.7), respectively. Likewise for milk sensitization, the adjusted prevalence in MACS of 2.4% (95% CI 1.6-3.1) was comparable to the observed prevalence in high-risk HealthNuts, 2.6% (95% CI

TABLE I. Comparison of demographic characteristics between “high-risk” HealthNuts and MACS cohorts using the MACS sampling frame (high risk ≥ 1 family member with allergy)

Characteristic	MACS (%) (n = 620)	High-risk HealthNuts (%) (n = 3,661)	P value
Maternal allergy			
Asthma	43.4	21.5	<.001
Hay fever	60.7	44.2	<.001
Eczema	38.9	20.3	<.001
Food allergy	38.9	8.1	<.001
Any allergy	82.9	63.7	<.001
Paternal allergy			
Asthma	25.7	19.5	<.001
Hay fever	46.2	39.2	.001
Eczema	20.5	11.0	<.001
Food allergy	21.1	5.2	<.001
Any allergy	61.3	54.7	.002
Parental allergy			
Asthma	61.4	38.0	<.001
Hay fever	86.9	80.2	<.001
Eczema	54.6	29.7	<.001
Food allergy	51.0	12.8	<.001
Any allergy	94.4	83.3	<.001
Sibling allergy (among those with siblings)			
Asthma	59.0	19.0	<.001
Hay fever	36.4	12.5	<.001
Eczema	64.2	37.1	<.001
Food allergy	62.5	11.9	<.001
Any allergy	90.0	54.2	<.001
Sibling allergy			
No siblings	40.2	46.3	<.001
Siblings with no allergy	6.0	24.6	
Siblings with any allergy	53.9	29.0	
No. of immediate family members with allergy			
None	—	—	
One	25.2	58.6	<.001
Two	51.6	34.3	
Three or more	23.2	7.1	
Sex (male)	51.3	50.1	.57
Eczema diagnosis in first year*	15.0	29.7	<.001
Eczema diagnosis or use of topical steroids for rash in first year†	36.0	35.1	.67
No. of siblings			
None	40.2	46.3	.001
One	32.3	34.2	
Two	19.5	14.1	
Three or more	8.0	5.4	
Parent's country of birth			
Both Australian	72.9	63.2	<.001
One or both Asian	3.1	13.4	
Other	24.0	23.4	

MACS, Melbourne Atopy Cohort Study.

*Parent report of a doctor diagnosis of eczema.

†Parent report of a doctor diagnosis of eczema or topical steroid use of an itchy rash excluding the scalp or nappy area.

2.0-3.4). CIs for comparisons overlapped, indicating that the prevalence of food sensitization among high-risk infants has remained stable between the 2 cohorts. In the sensitivity analysis, which included eczema (diagnosis or use of topical steroids for an itchy rash) as a covariate in the regression model, the adjusted prevalence of sensitization in MACS was, again, very similar to the observed prevalence of food sensitization in the high-risk subgroup of HealthNuts (data not shown).

Likewise, the observed prevalence of SPT $\geq 95\%$ PPVs was higher in the MACS cohort, but after standardization to the HealthNuts cohort, the prevalence was similar (Figure 2 and Table II). The observed prevalence of SPT $\geq 95\%$ PPVs in high-risk HealthNuts and adjusted prevalence in MACS were 2.1% (95% CI 1.7-2.6) and 2.0% (95% CI 1.5-2.6) respectively for peanut, 7.2% (95% CI 6.4-8.1) and 7.1% (95% CI 6.0-8.3) respectively for egg, and 0.1% (95% CI 0.03-0.4) and 0.2% (95% CI 0-0.4) respectively for cow's milk. To ensure reliability of our results, we also standardized the prevalence of sensitization in the HealthNuts population-based cohort to reflect the MACS cohort and compared the adjusted high-risk HealthNuts prevalence with the observed MACS prevalence; the proportions were similar and all CIs overlapped between comparisons (Table II).

DISCUSSION

The prevalence of food sensitization among high-risk infants with a family history of allergic disease has not changed significantly over the last 2 decades in Melbourne, Australia. In addition, we found that the proportion of high-risk infants with a proxy for clinical food allergy (SPT $\geq 95\%$ PPVs) also remained stable during this period. These findings are surprising given the increased anaphylaxis admission rates and increased reported diagnoses of food allergy in Australia and internationally.^{4-6,8,10,11,21}

Within Australia, hospital admission for anaphylaxis and referrals to allergy specialists have increased over recent decades.^{4,6} Doctor-diagnosed food allergy (on the basis of SPT and clinical history) within 1 clinic that provided half the regional ambulatory allergy-related services in the Australian Capital Territory and assessed 18,028 patients between 1995 and 2007 reported a 10-fold increase in food allergy diagnoses.⁵ In the USA and UK, self-reported food allergy and food allergy-related health care utilization (ambulatory care visits to hospitals, physician offices, and hospitalizations) have also increased over the last 1 to 2 decades.^{8,10,21} It is important to note that markers that reflect health care utilization, such as hospital admissions, cannot differentiate between increased episodes in the same pool of individuals versus increased number of individuals having the same number of episodes, and therefore it is important to assess markers that describe the number of affected individuals in the population, such as food allergy and sensitization rates. In the UK, 2 birth cohorts recruited in the same location 12 years apart reported an increase in clinical peanut allergy at age 10 years from 0.58% in 1999 to 1.5% in 2011-2012; however, this difference failed to reach statistical significance ($P = .09$). Different methods were used to define peanut allergy; SPT and clinical history were used in both cohorts, but the latter also included food challenges.¹³ In Montreal, 2 repeated cross-sectional studies of school children assessed time trends in peanut allergy between 2000-2002 ($n = 4,339$) and 2005-2007 ($n = 5,161$). The studies consisted of a parental questionnaire to

TABLE II. The observed proportion and adjusted prevalence of sensitization and SPT $\geq$ 95% PPVs in 2 cohorts of 12-month-old infants

(A) Egg				
	Whole HealthNuts (n = 5,139)	Low-risk HealthNuts (n = 1,577)	High-risk HealthNuts (n = 3,562)	High-risk MACS (n = 541)
Egg SPT $\geq$ 2 mm				
Observed proportion	13.5 (12.6-14.5)	11.3 (9.8-12.9)	14.5 (13.4-15.7)	19.4 (16.3-23.0)
Prevalence adjusted to HealthNuts model	—	—	—	15.0 (13.4-16.6)
Prevalence adjusted to MACS model	16.9 (13.0-20.7)	13.8 (8.4-19.3)	18.2 (14.7-21.7)	—
Egg SPT $\geq$ 4 mm				
Observed proportion	6.8 (6.2-7.6)	6.1 (5.0-7.4)	7.2 (6.4-8.1)	16.3 (13.4-19.6)
Prevalence adjusted to HealthNuts model	—	—	—	7.1 (6.0-8.3)
Prevalence adjusted to MACS model	13.5 (9.9-17.1)	10.7 (5.8-15.6)	14.8 (11.5-18.1)	—
(B) Peanut				
	Whole HealthNuts (n = 5139)	Low-risk HealthNuts (n = 1579)	High-risk HealthNuts (n = 3562)	High-risk MACS (n = 541)
Peanut SPT $\geq$ 2 mm				
Observed proportion	7.6 (6.9-8.3)	6.9 (5.8-8.3)	7.9 (7.0-8.8)	14.4 (11.7-17.6)
Prevalence adjusted to HealthNuts model	—	—	—	7.9 (6.8-8.9)
Prevalence adjusted to MACS model	13.8 (10.8-16.8)	12.4 (9.1-15.6)	14.4 (11.4-17.4)	—
Peanut SPT $\geq$ 8 mm				
Observed proportion	2.0 (1.6-2.4)	1.7 (1.1-2.5)	2.1 (1.7-2.6)	3.3 (2.1-5.2)
Prevalence adjusted to HealthNuts model	—	—	—	2.0 (1.5-2.6)
Prevalence adjusted to MACS model	4.4 (2.2-6.5)	4.3 (1.8-6.7)	4.4 (2.3-6.5)	—
(C) Milk				
	Whole HealthNuts (n = 2725)	Low-risk HealthNuts (n = 832)	High-risk HealthNuts (n = 1893)	MACS (n = 541)
Milk SPT $\geq$ 2mm				
Observed proportion	2.2 (1.7-2.8)	1.2 (0.6-2.2)	2.6 (2.0-3.4)	8.5 (6.4-11.2)
Prevalence adjusted to HealthNuts model	—	—	—	2.4 (1.6-3.1)
Prevalence adjusted to MACS model	9.1 (6.3-11.9)	8.6 (5.3-11.9)	9.3 (6.6-12.0)	—
Milk SPT $\geq$ 8 mm				
Observed proportion	0.1 (0.03-0.3)	0.1 (0.01-0.9)	0.1 (0.03-0.4)	1.3 (0.6-2.7)
Prevalence adjusted to HealthNuts model	—	—	—	0.2 (0.0-0.4)
Prevalence adjusted to MACS model	0.7 (0.03-1.3)	0.3 (0.0-0.7)	0.9 (0.09-1.6)	—

MACS, Melbourne Atopy Cohort Study; PPV, positive predictive value; SPT, skin prick test.

The adjusted MACS prevalence maintained the distribution of covariates in MACS, but assumed the same association between exposures (covariates) and outcomes as in HealthNuts. Similarly, the adjusted HealthNuts prevalence maintained the same covariate distribution in HealthNuts, but assumed the same association between exposure (covariates) and outcomes as in MACS. The primary comparison was between the observed prevalence in high-risk HealthNuts and adjusted prevalence in MACS (shown in bold).

determine peanut tolerance and corroboratory SPT/sIgE in those with a convincing or uncertain history of peanut allergy or insufficient peanut ingestion to determine peanut tolerance. The prevalence of peanut allergy was similar between 2000-2002 and 2005-2007, at 1.34% and 1.62%, and the authors suggested that food allergy rates may be stabilizing.²² In China, 2 cross-sectional studies conducted in 1999 and 2009 found that the prevalence of challenge-confirmed food allergy in infants under 2 years of age rose from 3.5% in 1999 to 7.7% in 2009 ($P = .02$). Interestingly, the prevalence of parent-reported food allergy did not increase significantly over this same period.¹¹

We offer several explanations for this apparent paradox, if we assume that the prevalence of food sensitization has not changed among high-risk infants. The increase in food allergy could be due to an increase in food allergy in the low-risk group, changes in the relationship between food sensitization and food allergy, or an increase in the proportion of high-risk infants in the population. Alternatively, the apparent increase in food allergy could

reflect changes in reporting and awareness of food allergy or increased number or severity of reactions in an unchanged number of affected individuals.

Given that the prevalence of food sensitization has not changed, the reported increase in food allergy could be due to an increase in food allergy in the low-risk group that may be driven by differences in the distribution or magnitude of the association between environmental risk factors and the risk of food allergy. This hypothesis is supported by recent findings from the population-based HealthNuts study, which showed that the family history is not a strong driver of food allergy, as the risk of challenge-confirmed food allergy only increased 1.4-fold if the infant had 1 family member with a history of allergic disease, and by 1.8-fold if the infant had 2 or more family members with a history of allergic disease.²³ Environmental risk factors also appear to play a stronger role in those who are at low risk of food allergy, for example, delaying the introduction of allergenic foods into the infant diet had a stronger magnitude of association

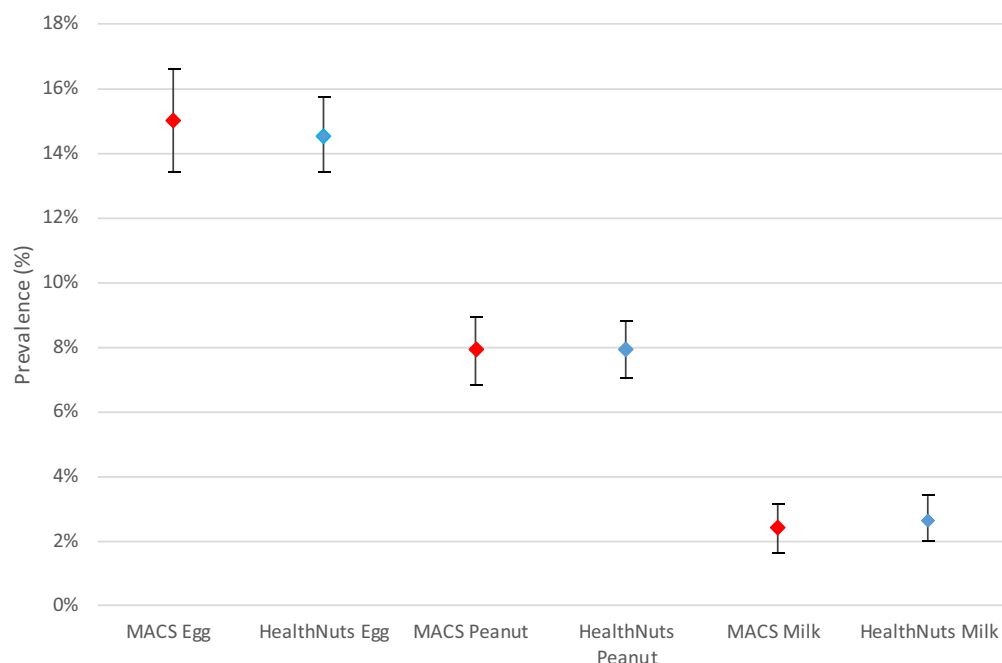


FIGURE 1. The adjusted prevalence of sensitization in MACS (1990-1994) and the observed prevalence of sensitization in high-risk HealthNuts (2007-2011). *MACS*, Melbourne Atopy Cohort Study.

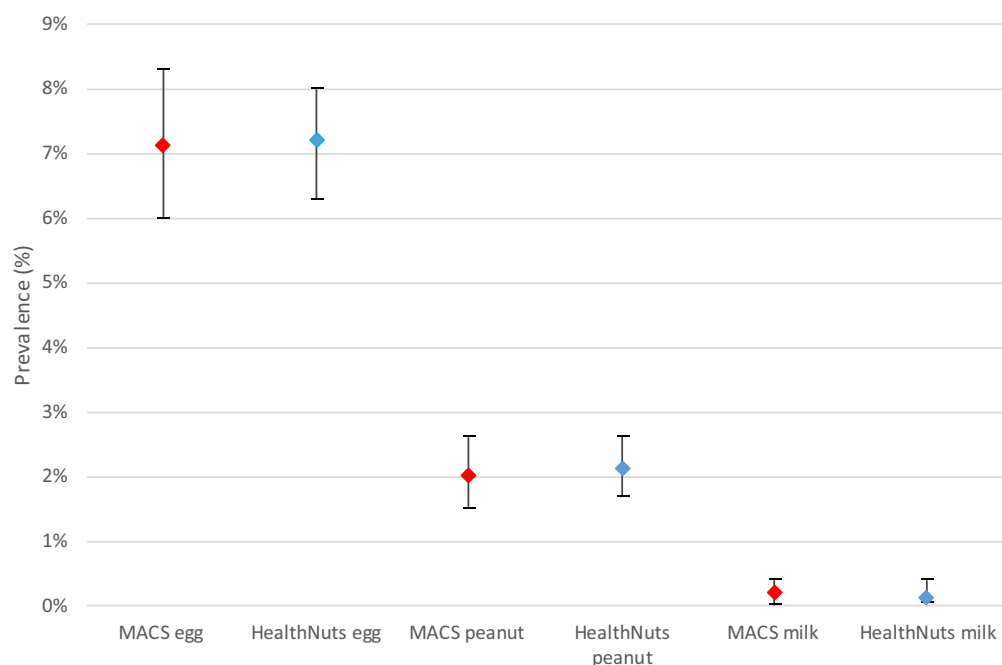


FIGURE 2. The adjusted prevalence of SPT $\geq$ 95% PPV for food allergy in MACS (1990-1994) and the observed prevalence of sensitization in high-risk HealthNuts (2007-2011). *MACS*, Melbourne Atopy Cohort Study.

among low-risk infants compared with high-risk infants. Compared with introducing egg into the infant's diet at 4 to 6 months, delaying the introduction of egg in low-risk infants (without a family history of food allergy, or a personal history of eczema or food reactions) until 10 to 12 months increased the risk of egg allergy (adjusted odds ratio 3.3; 95% CI 1.1-9.9),

whereas it was not associated with egg allergy in high-risk infants (adjusted odds ratio 1.4; 95% CI 0.9-2.4). The risk of egg allergy in high-risk infants was only increased if the delayed introduction of egg was prolonged until after 12 months of age.²⁴ In addition, infants living in Australia whose parents were born in Asia have a higher risk of food allergies, yet paradoxically, there were lower

rates of allergic disease among Asian parents.²⁵ Therefore, the rise in food allergy could be due to a change in distribution or magnitude of association of environmental factors associated with food allergy including eczema, household size, pet exposure, vitamin D insufficiency, increased Asian migration to Australia and timing of introduction solids.²⁴⁻²⁸

In the present comparison, we observed higher rates of Asian heritage in HealthNuts compared with MACS, which is a known risk factor for eczema and food allergy particularly in the Australian population.^{25,26,29} A history of eczema is one of the strongest known risk factors for food allergy. Skin barrier dysfunction, a feature of eczema, is postulated to play an important role in the initiation of allergic sensitization and subsequent progression to food allergy and other allergic disease.³⁰ Although a higher prevalence of doctor-diagnosed eczema was observed in the more recent population-based HealthNuts compared with high-risk MACS, which may reflect increased health-seeking behavior because of concerns and awareness about allergies or increased awareness and diagnosis by physicians, the prevalence of the more sensitive definition of eczema, which included both a doctor's diagnosis and topical steroid use for an itchy rash, was similar. In addition, inclusion of eczema in the standardization procedure, as described in the sensitivity analysis, did not materially alter our results. Differences in infant feeding patterns were observed between the 2 studies. In MACS, parents were advised to delay the introduction of allergenic foods such as egg and peanut until after 12 months of age, as per the infant feeding guidelines at the time. Midway through recruitment of the HealthNuts cohort these guidelines were altered to remove the advice to delay the introduction of allergenic solids. As such, infants in HealthNuts were introduced to egg earlier than in MACS, with 95% and 28% having been introduced to egg and peanut respectively by the age of 12 months, compared with only 6% and 2% respectively in MACS. The delayed introduction of allergenic foods in MACS, unlike HealthNuts, may have contributed to a higher prevalence of sensitization in the earlier study.

Another possible explanation for the apparent rise in food allergy given stable sensitization rates is that the conversion from food sensitization to food allergy has changed, and that more infants are exposed to risk factors that allow manifestation of food allergy amongst the population of sensitized infants. This explanation was also proposed by the authors of the US study showing stable sIgE rates over time.¹² In the Learning Early About Peanut allergy trial, conversion from peanut sensitization to peanut allergy differed by peanut exposure groups; among 98 peanut sensitized infants (SPT 1-4 mm), 35.3% of those who avoided peanut developed peanut allergy compared with only 10.6% of those who frequently ingested peanut.^{12,31} We did not find any evidence in the HealthNuts study to suggest that the conversion from food sensitization to food allergy differed between low- and high-risk infants (data not shown); however, we do not have data on low-risk infants at the time of the MACS study to inform whether this has changed over time. Previous research has focused on risk factors for food sensitization or food allergy, but few studies have explored risk factors for the conversion from food sensitization to challenge-confirmed food allergy.

The reported increase in food allergy could also be due to an increase in the high-risk proportion of the population. The HealthNuts cohort is population based and has good external validity to the general population of Victorian infants born at

that time.¹⁹ Nearly 70% of this cohort met the criteria for being at high risk of food allergy by having an immediate family member with a history of allergic disease. As MACS recruited only high-risk infants, it was not clear what proportion of the general population they represented. It was estimated that it represented 19.3% of the general population when comparing characteristics with those of another birth cohort recruited elsewhere in Australia at the same time.³² In addition, the prevalence of other allergic diseases (asthma, eczema, allergic rhinitis) is reported to have increased over last 50 years, reaching a plateau around the 1990s. This suggests an increase in allergic disease in the parent populations of the 2 cohorts increasing the proportion of the population at high risk of food allergy.

An alternative explanation is that food allergy may not be on the rise, and any apparent increase is due to increased awareness, increased diagnosis, or increased number or severity of reactions among the food allergic population. There is a lack of repeated, cross-sectional food allergy prevalence studies, and instead data suggesting that food allergy has increased in Australia originates from studies on hospital admissions for anaphylaxis, referrals for allergy services, and doctor diagnoses of food allergy. Between 1994 and 2005 hospital admissions for food-related anaphylaxis doubled, and this increase was most notable in the age group of 0 to 4 years, where a 5.5-fold increase was observed.⁹ This may reflect increased severity of food allergy or an increased number of reactions among food allergic individuals, rather than increased prevalence.

Mullins et al published a retrospective review of more than 18,000 referrals to a single center that provided half the ambulatory allergy-related services in the Australian Capital Territory and included 778 patients diagnosed with peanut allergy. They reported that food allergy and peanut allergy diagnoses rose 10-fold from 1995 to 2007, yet there was no difference in severity of reactions or anaphylaxis among patients with peanut allergy over this period. This may also reflect increased awareness and therefore referrals for food allergy assessment, rather than only increased prevalence. This study also reported that peanut sensitization rose during this period; however, SPT were not systematically performed on all patients, only those suspected of food allergy based on personal or family history, so this increase may reflect increased awareness and testing for food allergy.⁵ Interestingly, there was no increase in parent-reported food allergy in repeated cross-sectional studies in China that showed an increase in challenge-confirmed food allergy.¹¹

The strengths of this study are that we have assessed the prevalence of food sensitization in 2 cohorts in the same geographic region using similar methods to define sensitization. The HealthNuts sample is large, population based, and has good external validity.¹⁹ In addition, we have assessed this in infancy, where the prevalence of food sensitization is likely to be at its highest considering that egg and milk allergy are frequently outgrown in childhood.

A limitation of this study is that different recruitment strategies and eligibility criteria were used to recruit the 2 cohorts. However, the study designs allowed for measurement and assessment of key demographic factors that differed between the 2 cohorts. In this case, our samples differed in terms of the family history of allergic disease based on the sampling criteria suggesting that we have not fully captured the actual "algorithm" used to recruit and admit people to the MACS study. Despite applying the MACS sampling criteria to HealthNuts to achieve a

similar cohort (infants with an immediate family member with a history of allergic disease), the MACS cohort still had a higher number of family members with an allergic disease compared with the high-risk HealthNuts subgroup. Although the proportion of infants with SPT $\geq$ 95% PPVs was similar between the 2 cohorts, another limitation is that we are unable to assess the prevalence of true food allergy using challenge-proven outcomes between the 2 groups. In addition, we have compared the prevalence from a high-risk cohort born in the early 1990s with a high-risk subgroup from a population-based study born 2006–2010. Unfortunately, we do not have population-based data from the early 1990s and are unable to compare time trends of the prevalence of sensitization at the population level nor between low-risk infants.

In conclusion, we report that the prevalence of food sensitization among high-risk infants has remained stable in Melbourne, Australia, since the 1990s, which does not explain the apparent increase in food allergy and food-related anaphylaxis reported during the same time period in this region. Given that sensitization has not changed, the increase in food allergy could be due to an increase in the high-risk proportion of the population, differences in the prevalence or magnitude of association between environmental risk factors and the risk of food allergy in the low-risk group, or changes in the relationship between food sensitization and food allergy. An alternative explanation is that food allergy may not be on the rise and the apparent increase is due to increased awareness, informal self-reported diagnosis, formal diagnosis by health professionals, or increased number or severity of reactions, particularly anaphylaxis.

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REFERENCES

- Prescott S, Allen KJ. Food allergy: riding the second wave of the allergy epidemic. *Pediatr Allergy Immunol* 2011;22:155-60.
- Ben-Shoshan M, Turnbull E, Clarke A. Food allergy: temporal trends and determinants. *Curr Allergy Asthma Rep* 2012;12:346-72.
- Liew WK, Williamson E, Tang ML. Anaphylaxis fatalities and admissions in Australia. *J Allergy Clin Immunol* 2009;123:434-42.
- Mullins RJ. Paediatric food allergy trends in a community-based specialist allergy practice, 1995-2006. *Med J Aust* 2007;186:618-21.
- Mullins RJ, Dear KB, Tang ML. Characteristics of childhood peanut allergy in the Australian Capital Territory, 1995 to 2007. *J Allergy Clin Immunol* 2009;123:689-93.
- Mullins RJ, Dear KB, Tang ML. Time trends in Australian hospital anaphylaxis admissions in 1998-1999 to 2011-2012. *J Allergy Clin Immunol* 2015;136:367-75.
- Poulos LM, Waters AM, Correll PK, Loblay RH, Marks GB. Trends in hospitalizations for anaphylaxis, angioedema, and urticaria in Australia, 1993-1994 to 2004-2005. *J Allergy Clin Immunol* 2007;120:878-84.
- Sicherer SH, Munoz-Furlong A, Godbold JH, Sampson HA. US prevalence of self-reported peanut, tree nut, and sesame allergy: 11-year follow-up. *J Allergy Clin Immunol* 2010;125:1322-6.
- Venter C, Hasan Arshad S, Grundy J, Pereira B, Bernie Clayton C, Voigt K, et al. Time trends in the prevalence of peanut allergy: three cohorts of children from the same geographical location in the UK. *Allergy* 2010;65:103-8.
- Branum AM, Lukacs SL. Food allergy among children in the United States. *Pediatrics* 2009;124:1549-55.
- Hu Y, Chen J, Li H. Comparison of food allergy prevalence among Chinese infants in Chongqing, 2009 versus 1999. *Pediatr Int* 2010;52:820-4.
- McGowan EC, Peng RD, Salo PM, Zeldin DC, Keet CA. Changes in food-specific IgE over time in the National Health and Nutrition Examination Survey (NHANES). *J Allergy Clin Immunol Pract* 2016;4:713-20.
- Venter C, Maslin K, Patil V, Kurukulaaratchy R, Grundy J, Glasbey G, et al. The prevalence, natural history and time trends of peanut allergy over the first 10 years of life in two cohorts born in the same geographical location 12 years apart. *Pediatr Allergy Immunol* 2016;27:804-11.
- Peters RL, Koplin JJ, Gurrin LC, Dharmage SC, Wake M, Ponsonby AL, et al. The prevalence of food allergy and other allergic diseases in early childhood in a population-based study: HealthNuts age 4-year follow-up. *J Allergy Clin Immunol* 2017;140:145-153.e8.
- Lowe AJ, Lodge CJ, Allen KJ, Abramson MJ, Matheson MC, Thomas PS, et al. Cohort profile: Melbourne Atopy Cohort study (MACS). *Int J Epidemiol* 2017;46:25-6.
- Koplin JJ, Wake M, Dharmage SC, Matheson M, Tang ML, Gurrin LC, et al. Cohort profile: The HealthNuts Study: population prevalence and environmental/genetic predictors of food allergy. *Int J Epidemiol* 2015;44:1161-71.
- Peters RL, Allen KJ, Dharmage SC, Tang ML, Koplin JJ, Ponsonby AL, et al. Skin prick test responses and allergen-specific IgE levels as predictors of peanut, egg, and sesame allergy in infants. *J Allergy Clin Immunol* 2013;132:874-80.
- Alduraywish SA, Lodge CJ, Vicendese D, Lowe AJ, Erbas B, Matheson MC, et al. Sensitization to milk, egg and peanut from birth to 18 years: a longitudinal study of a cohort at risk of allergic disease. *Pediatr Allergy Immunol* 2016;27:83-91.
- Osborne NJ, Koplin JJ, Martin PE, Gurrin LC, Thiele L, Tang ML, et al. The HealthNuts population-based study of paediatric food allergy: validity, safety and acceptability. *Clin Exp Allergy* 2010;40:1516-22.
- Moreno-Betancur M, Koplin JJ, Ponsonby AL, Lynch J, Carlin JB. Measuring the impact of differences in risk factor distributions on cross-population differences in disease occurrence: a causal approach. *Int J Epidemiol* 2018;47:217-25.
- Kotz D, Simpson CR, Sheikh A. Incidence, prevalence, and trends of general practitioner-recorded diagnosis of peanut allergy in England, 2001 to 2005. *J Allergy Clin Immunol* 2011;127:623-630.e1.
- Ben-Shoshan M, Kagan RS, Alizadehfar R, Joseph L, Turnbull E, St Pierre Y, et al. Is the prevalence of peanut allergy increasing? A 5-year follow-up study in children in Montreal. *J Allergy Clin Immunol* 2009;123:783-8.
- Koplin JJ, Allen KJ, Gurrin LC, Peters RL, Lowe AJ, Tang ML, et al. The impact of family history of allergy on risk of food allergy: a population-based study of infants. *Int J Environ Res Public Health* 2013;10:5364-77.
- Koplin JJ, Osborne NJ, Wake M, Martin PE, Gurrin LC, Robinson MN, et al. Can early introduction of egg prevent egg allergy in infants? A population-based study. *J Allergy Clin Immunol* 2010;126:807-13.
- Koplin JJ, Peters RL, Ponsonby AL, Gurrin LC, Hill D, Tang ML, et al. Increased risk of peanut allergy in infants of Asian-born parents compared to those of Australian-born parents. *Allergy* 2014;69:1639-47.
- Panjari M, Koplin JJ, Dharmage SC, Peters RL, Gurrin LC, Sawyer SM, et al. Nut allergy prevalence and differences between Asian-born children and Australian-born children of Asian descent: a state-wide survey of children at primary school entry in Victoria, Australia. *Clin Exp Allergy* 2016;46:602-9.
- Allen KJ, Koplin JJ, Ponsonby AL, Gurrin LC, Wake M, Vuillermin P, et al. Vitamin D insufficiency is associated with challenge-proven food allergy in infants. *J Allergy Clin Immunol* 2013;131:1109-16. 1116.e1-6.
- Koplin JJ, Dharmage SC, Ponsonby AL, Tang ML, Lowe AJ, Gurrin LC, et al. Environmental and demographic risk factors for egg allergy in a population-based study of infants. *Allergy* 2012;67:1415-22.

29. Martin PE, Koplin JJ, Eckert JK, Lowe AJ, Ponsonby AL, Osborne NJ, et al. The prevalence and socio-demographic risk factors of clinical eczema in infancy: a population-based observational study. *Clin Exp Allergy* 2013;43:642-51.
30. Dharmage SC, Lowe AJ, Matheson MC, Burgess JA, Allen KJ, Abramson MJ. Atopic dermatitis and the atopic march revisited. *Allergy* 2014;69:17-27.
31. Du Toit G, Roberts G, Sayre PH, Bahnson HT, Radulovic S, Santos AF, et al. Randomized trial of peanut consumption in infants at risk for peanut allergy. *N Engl J Med* 2015;372:803-13.
32. Hill DJ, Hosking CS, Zhie CY, Leung R, Baratwidjaja K, Iikura Y, et al. The frequency of food allergy in Australia and Asia. *Environ Toxicol Pharmacol* 1997;4:101-10.

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TABLE E1. Logistic regression models that were used in the standardization procedure

Exposure	Adjusted odds ratio	P value
(A) Egg sensitization		
Study indicator (HealthNuts)	0.84 (0.52-1.35)	.466
Sex (female)	0.83 (0.71-0.97)	.016
Maternal asthma	1.33 (1.08-1.63)	.007
Maternal eczema	1.39 (1.13-1.7)	.002
Maternal hay fever	0.86 (0.54-1.34)	.499
Maternal hay fever and study interaction	1.4 (0.86-2.26)	.176
Paternal asthma	1.67 (1.01-2.75)	.044
Paternal asthma and study interaction	0.7 (0.4-1.21)	.202
Paternal hay fever	1.69 (1.05-2.71)	.029
Paternal hay fever and study interaction	0.64 (0.39-1.07)	.09
Paternal eczema	1.42 (1.1-1.83)	.007
Parent's country of birth (both Australian)	1.0	—
One or both Asian	2.89 (2.37-3.54)	<.001
Other	1.34 (1.11-1.62)	.002
(B) Egg SPT $\geq$ 4 mm		
Study indicator (HealthNuts)	0.54 (0.32-0.93)	.026
Sex (female)	0.72 (0.59-0.89)	.002
Maternal asthma	1.27 (0.97-1.66)	.077
Maternal eczema	1.42 (1.09-1.84)	.009
Maternal hay fever	0.84 (0.51-1.36)	.471
Maternal hay fever and study interaction	1.48 (0.86-2.53)	.157
Paternal asthma	2.05 (1.2-3.51)	.009
Paternal asthma and study interaction	0.46 (0.24-0.88)	.018
Paternal hay fever	1.6 (0.95-2.68)	.077
Paternal hay fever and study interaction	0.62 (0.35-1.11)	.105
Paternal eczema	1.69 (0.97-2.94)	.064
Paternal eczema and study interaction	0.72 (0.36-1.44)	.354
Parent's country of birth (both Australian)	1.0	—
One or both Asian	2.77 (2.12-3.61)	<.001
Other	1.41 (1.1-1.8)	.006
(C) Peanut sensitization		
Study indicator (HealthNuts)	0.5 (0.38-0.67)	<.001
Sex (female)	0.64 (0.53-0.78)	<.001
Maternal asthma	1.34 (1.04-1.72)	.023
Maternal hay fever	1.27 (1.02-1.57)	.031
Paternal asthma	1.33 (1.02-1.73)	.036
Paternal hay fever	1.28 (1.03-1.59)	.023
Parent's country of birth (both Australian)	1.0	—
One or both Asian	3.34 (2.6-4.28)	<.001
Other	1.6 (1.26-2.02)	<.001
(D) Peanut SPT $\geq$ 8 mm		
Study indicator (HealthNuts)	0.38 (0.21-0.69)	.002
Sex (female)	0.66 (0.45-0.96)	.03
Maternal asthma	0.43 (0.14-1.34)	.145
Maternal asthma and study interaction	3.71 (1.07-12.79)	.038
Paternal hay fever	1.97 (1.35-2.87)	<.001
Parent's country of birth (both Australian)	1.0	—
One or both Asian	3.85 (2.47-6.01)	<.001
Other	1.6 (1.01-2.54)	.045

(continued)

TABLE E1. (Continued)

Exposure	Adjusted odds ratio	P value
(E) Cow's milk sensitization		
Study indicator (HealthNuts)	0.2 (0.13-0.32)	<.001
Sex (female)	0.84 (0.57-1.25)	.4
Paternal asthma	1.55 (0.95-2.53)	.081
Paternal eczema	0.79 (0.36-1.72)	.545
Paternal eczema and study interaction	2.48 (0.86-7.16)	.092
Paternal hay fever	1.34 (0.87-2.05)	.186
Parent's country of birth (both Australian)	1.0	—
One or both Asian	2.59 (1.51-4.46)	.001
Other	1.27 (0.79-2.05)	.327
(F) Cow's milk SPT $\geq$ 8 mm		
Study indicator (HealthNuts)	0.15 (0.03-0.67)	.013
Maternal eczema	6.24 (1.51-25.83)	.012
Maternal food allergy	0.83 (0.19-3.58)	.802
Paternal hay fever	2.63 (0.73-9.57)	.141

SPT, Skin prick test.

TABLE E2. Comparison of demographic characteristics between the whole HealthNuts and MACS cohorts

	MACS (n = 620)	HealthNuts (n = 5,276)	P value
Maternal allergy			
Asthma	43.3	14.9	<.001
Hay fever	60.7	30.7	<.001
Eczema	38.9	14.1	<.001
Food allergy	38.6	5.6	<.001
Any allergy	82.9	44.2	<.001
Paternal allergy			
Asthma	25.7	13.6	<.001
Hay fever	46.2	27.2	<.001
Eczema	20.5	7.6	<.001
Food allergy	21.1	3.6	<.001
Any allergy	61.3	37.9	<.001
Parental allergy			
Asthma	61.4	26.4	<.001
Hay fever	86.9	55.6	<.001
Eczema	54.6	20.6	<.001
Food allergy	51.0	8.9	<.001
Any allergy	94.3	57.8	<.001
Sibling allergy (among those with siblings)			
Asthma	59.0	14.1	<.001
Hay fever	36.4	9.3	<.001
Eczema	64.2	27.4	<.001
Food allergy	62.5	8.8	<.001
Any allergy	90.0	40.1	<.001
Sibling allergy			
No siblings	40.2	49.6	<.001
Siblings with no allergy	6.0	30.2	
Siblings with any allergy	53.9	20.2	
Number of immediate family members with allergy			
None	0	30.6	<.001
One	25.2	40.6	
Two	51.6	23.8	
Three or more	23.2	5.0	
Sex (male)	51.3	50.9	.85
Eczema diagnosis in first year*	15.0	26.6	<.001
Eczema diagnosis or use of topical steroids for rash in first year†	36.0	31.5	.03
Mother current smoker	6.3	5.7	.57
Father current smoker	18.2	15.3	.06
Parent's country of birth			
Both Australian	72.9	59.2	<.001
One or both Asian	3.1	15.9	
Other	24.0	24.9	

MACS, Melbourne Atopy Cohort Study.

*Parent's report of a doctor diagnosis of eczema in the first year of life.

†Parent report of a doctor diagnosis of eczema or topical steroid use of an itchy rash excluding the scalp or nappy area.

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