

Environmental and demographic risk factors for egg allergy in a population-based study of infants

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Abstract

Background: Although egg allergy is the most common food allergy in infants and young children, risk factors for egg allergy remain largely unknown. This study examined the relationship between environmental and demographic factors and egg allergy in a population-based infant cohort.

Methods: In a study of 5276 infants (HealthNuts), infants underwent skin prick testing (SPT) to egg white at 12 months of age. Questionnaire data on relevant exposures were obtained. 699/873 (80%) infants eligible for oral food challenge (detectable wheal on SPT) attended for formal assessment of egg allergy status; 453 had confirmed egg allergy (positive challenge and SPT ≥ 2 mm). Associations between environmental and demographic factors and egg allergy were investigated using multivariable logistic regression.

Results: Children with older siblings and those with a pet dog at home were less likely to develop egg allergy by 1 year of age (adjusted OR [aOR], 0.72; 95% CI, 0.62, 0.83 per sibling; and aOR, 0.72; 95% CI, 0.52, 0.99, respectively). Caesarean section delivery, antibiotic use in infancy, childcare attendance and maternal age were not associated with egg allergy. History of allergic disease in an immediate family member and having parents born in East Asia were strong risk factors for infantile egg allergy (aOR, 1.82; 95% CI, 1.40, 2.36; and aOR, 3.30; 95% CI, 2.45, 4.45, respectively).

Conclusions: Exposure in the first year of life to siblings and dogs may decrease the risk of subsequent egg allergy. Infants with a family history of allergy and those with parents born in East Asia are at increased risk of egg allergy.

Food allergy in childhood is becoming increasingly common (1), affecting up to 10% of infants (2). Of particular concern is the notable increase in the incidence of hospital admissions for food allergy-related anaphylaxis, the most severe manifestation of food-induced allergy, in countries including the United States, the UK and Australia (3–5).

Egg allergy is one of the most prevalent IgE-mediated food allergies in infants and young children (2, 6). To date, risk factors for egg allergy remain largely unknown. Although egg allergy itself is usually outgrown, individuals with egg

allergy are at increased risk of developing other atopic manifestations such as asthma and allergic rhinitis later in life (7–9). An understanding of risk factors for egg allergy may therefore be valuable in understanding the development of chronic allergic diseases later in life.

Environmental factors that have been suggested to be associated with allergic disease include number of older siblings, contact with other children during childcare, exposure to pets, caesarean section delivery, infant diet, parents' country of birth, family history of allergy and use of antibiotics in infancy (10–16). No large

population-based studies to date have examined the role of all of these factors in the development of egg allergy during infancy.

We have previously shown that later introduction of egg (after 10 months of age) is strongly associated with risk of egg allergy, while duration of breastfeeding and age at introduction of solid foods do not appear to play an important role in the development of infant egg allergy (13). In this article, we investigate the role of other environmental and demographic factors in egg allergy using data from HealthNuts, a single-centre, population-based study of food allergy in over 5000 12-month-old infants using oral food challenges to confirm egg allergy.

Methods

HealthNuts study methods: recruitment of participants and assessment of egg allergy status

The HealthNuts study is a population-based study of infants recruited from council-led immunisation sessions in Melbourne, Australia, at the time of their 12-month immunisations. Recruitment took place between September 2007 and August 2011. All infants aged between 11 and 15 months (inclusive) attending council-led immunisation sessions were eligible for recruitment. Study methods have been described in detail elsewhere (17). Briefly, all participating infants underwent a community-based skin prick test (SPT) to four foods including egg white as well as positive (histamine) and negative (saline) controls (ALK, Madrid, Spain). Infants with any detectable reaction on egg SPT greater than the negative saline control (irrespective of wheal size) were invited for further follow-up in the HealthNuts allergy clinic, at which stage the SPT was repeated, allergen-specific IgE was measured with the ImmunoCAP System FEIA (Phadia AB, Uppsala, Sweden), and oral food challenges were performed to raw egg white.

We defined sensitisation as a SPT wheal size ≥ 2 mm (9, 18, 19) or allergen-specific IgE ≥ 0.35 kUA/l (18, 20).

Infants were classified into one of two mutually exclusive categories based on sensitisation and food challenge results:

No IgE-mediated egg allergy: Either not sensitised to egg white or egg sensitised but tolerant of formal egg challenge ($n = 4510$).

IgE-mediated egg allergy: Allergic on formal egg challenge ($n = 443$) or previous history of clear reaction to egg occurring within 1 month of a positive SPT or RAST ($n = 10$). Criteria for the definition of a positive OFC have been described previously (21). These criteria consisted of one or more objective signs (hives, vomiting, angioedema or anaphylaxis) occurring within 2 h of a dose of egg white.

Infants with a positive oral food challenge with no evidence of egg sensitisation (egg SPT < 2 mm and specific IgE to egg white < 0.35 kUA/l) were excluded from the primary analyses reported in this manuscript as their IgE-mediated egg allergy status was unclear ($n = 28$). However, a sensitivity analysis was conducted with these infants classified as egg allergic to determine whether this altered any of our findings (see below for further information on sensitivity analyses).

Information on exposures

Information on environmental and demographic factors was collected using a self-administered questionnaire at the time of recruitment into the study, completed prior to receiving the results of skin prick testing and prior to any subsequent clinical food allergy testing (see supplementary material). At the time of the study, the current Victorian Department of Human Services infant feeding guidelines recommended that timing of introduction of solids be delayed until after 6 months and that egg be introduced after 10 months of age.

Statistical analysis

We used a binary classification of IgE-mediated egg allergy as either 'present' or 'absent' as described above. The final multivariable models included all environmental and demographic risk factors that showed a P -value smaller than 0.1 in the univariate analysis. Other variables that did not meet this criteria were considered as potential confounders and were included in the final model if they altered the magnitude of the association between any of the primary exposures and egg allergy by $>10\%$. Other potential confounders considered were infant history of eczema and duration of breastfeeding. The model was also adjusted for timing of introduction of egg, which is strongly associated with risk of egg allergy in this cohort (13).

Exposure to siblings was analysed separately for school-aged siblings (6 years or older) compared with siblings younger than 6 years because intra-household effects could be expected to be stronger before the age of regular school attendance (22).

Attendance of childcare at 0–6 months of age was examined separately from attendance after 6 months as childcare attendance by 6 months of age has previously been found to be associated with other childhood allergic outcomes (eczema and asthma) (10, 11).

Models with and without interactions between pairs of exposure variables were compared using likelihood ratio tests.

Sensitivity analysis

A sensitivity analysis was performed to examine the likely effect of missing data on egg allergy status, and further sensitivity analyses were performed to test the robustness of our results when using different definitions for egg allergy (see supplementary material).

Stata release 11.0 (StataCorp, College Station, TX, USA) was used for all analyses.

Ethics approval

Ethics approval was obtained from the Victorian State Government Office for Children and Department of Human Services (reference no. 10/07) and the Royal Children's Hospital (reference no. 27047) Human Research Ethics Committees.

Results

Study participation rates, skin prick test and oral food challenge results to egg are provided in Fig. 1.

Female gender, preterm delivery (<37 weeks gestation), having older siblings, maternal smoking during pregnancy, and exposure to a pet cat or dog were all inversely associated with egg allergy. Infants with a parent or sibling with eczema, asthma or hay fever were more likely to be egg allergic, as were infants with a mother or father born in East Asia ($P < 0.10$; Table 1).

In a multivariate model that also included adjustment for age at introduction of egg into the infant diet, preterm delivery, having siblings and having a dog inside the house were all inversely associated with egg allergy, while having a family history of allergy or a parent born in East Asia were associated with an increased risk of egg allergy (Table 2). The risk of egg allergy was similar among infants with parents born in Europe and Australia. Male infants were more likely to be egg allergic. There appeared to be a dose-response effect for number of siblings, whereby infants with multiple siblings had a greater reduction in egg allergy risk. Among infants with one or more siblings, those with siblings under the age of 6 years were less likely to have egg allergy compared to those with siblings aged 6 or above after adjusting for number of siblings (OR, 0.60; 95% CI, 0.39, 0.92; $P = 0.021$).

In the unadjusted analysis, maternal smoking during pregnancy and low socio-economic status were inversely

associated with risk of infant egg allergy. However, these factors were no longer associated with egg allergy in the adjusted model (Table 2). Parents' country of birth, socio-economic status and age at introduction of egg were identified as confounders of the association between maternal smoking and infant egg allergy. Collectively these factors reduced the magnitude of the association between maternal smoking and infant egg allergy by 43%. Similarly, parents' country of birth, maternal smoking during pregnancy and age at introduction of egg were identified as confounders of the association between socio-economic status and infant egg allergy. Collectively these factors reduced the magnitude of the association between low socio-economic status and infant egg allergy by 19%. We investigated potential confounding by family and infant history of allergy in the relationship between dog ownership and egg allergy to determine whether the observed association could be explained by changes in behaviour related to history of allergic disease. Adjusting for family history of eczema, asthma, hay fever or food allergy changed the magnitude of the association between dog ownership and infant egg allergy by <2%. There was evidence of a protective effect of having a dog inside the house on egg allergy even among those with no family history of allergic disease (OR, 0.51; 95% CI, 0.27, 0.96). Infant eczema emerged as a confounder, reducing the magnitude of the association between dog ownership and egg allergy by 16%. However, having a dog inside the house remained inversely associated

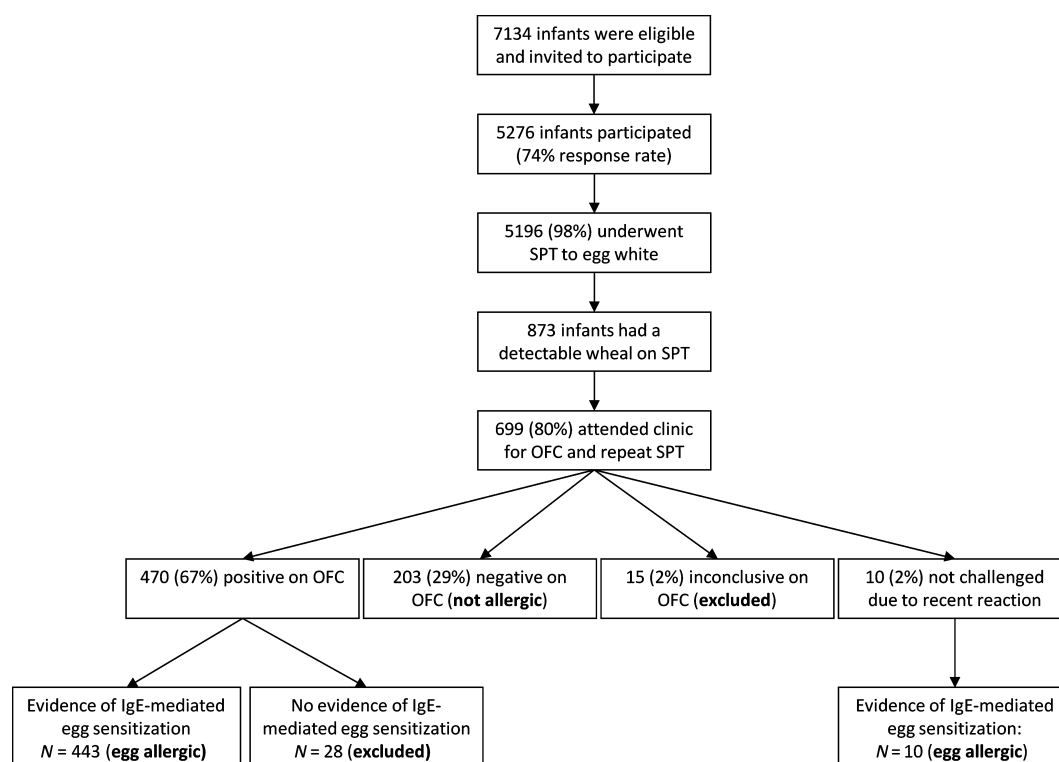


Figure 1 Response rates and classification of egg allergy status in the HealthNuts study.

Table 1 Demographic and lifestyle characteristics of infants participating in the HealthNuts study and their association with infant egg allergy ($N = 4963$)

	N^*	% Egg allergic	$P^†$
Gender			
Female	2512	10.1	0.018
Male	2423	8.2	
Mode of delivery			
Vaginal	3292	9.6	0.13
Caesarean section	1641	8.3	
Gestational age at delivery			
Term (>36 weeks)	4436	9.3	0.019
Pre-term (≤ 36 weeks)	289	5.2	
Number of siblings			
None	2420	10.8	<0.001
One	1641	8.3	
Two	631	7.0	
Three or more	217	3.7	
Childcare attendance			
Started > 12 months or not started	3501	9.2	0.28
Started 7–12 months	958	9.9	
Started 1–6 months	342	7.0	
Cat ownership in infancy			
No cats	4101	9.7	0.011
Cat outside only	166	7.8	
Cat allowed inside the house	693	6.2	
Dog ownership in infancy			
No dogs	351	10.2	<0.001
Dog outside only	41	8.1	
Dog allowed inside the house	60	5.9	
Use of antibiotics (age at first use)			
Never used antibiotics	2376	8.6	0.30
<3 months	245	10.6	
4–6 months	487	9.0	
7–9 months	473	11.2	
10–12 months	689	8.0	
Immediate family (parent/s or sibling/s) history of allergy:			
None	1521	6.7	<0.001
Eczema	1518	12.0	
Asthma	1515	10.5	0.027
Hay fever	2487	10.6	<0.001
Food allergy	625	10.9	0.10
County of birth of child's mother			
Australia	3531	7.9	<0.001
Europe	443	10.4	
East Asia	441	19.5	
Other	425	7.8	
Country of birth of child's father			
Australia	3392	7.8	<0.001
Europe	422	10.2	

Table 1 (continued)

	N^*	% Egg allergic	$P^†$
East Asia	340	22.1	<0.001
Other	662	8.6	
Socio-economic status			
Quintile 1 (most disadvantaged)	998	7.0	0.056
Quintile 2	993	10.3	
Quintile 3	1045	8.5	
Quintile 4	962	9.8	
Quintile 5 (least disadvantaged)	951	10.2	
Maternal smoking during pregnancy			
No	4593	9.4	0.003
Yes	228	3.5	
Maternal age at child's birth (mean, years)	4826	Mean 33.0	0.66

*Numbers may not add up to total because of missing data.

† P -values derived from Pearson's χ^2 tests for categorical variables and t -test for continuous variables.

Egg allergy was defined as a positive OFC in the context of IgE-mediated egg sensitisation.

with egg allergy even after adjustment for infant eczema (OR, 0.72; $P = 0.043$; Table 2). Additionally, dog ownership was associated with egg allergy among infant without a history of eczema (OR, 0.59; 95% CI, 0.38, 0.91).

Further adjustment for other variables not included in the final model, namely duration of breastfeeding, mode of delivery, use of antibiotics and childcare attendance, changed the magnitude of the reported association between each exposure variable and egg allergy by <10%. Evidence for an association between preterm delivery, number of siblings, dog ownership, family history of allergy and parents' country of birth remained after excluding infants with a parent-reported reaction to egg (data not shown).

We tested for interactions between pairs of exposure variables; however, no interactions were identified. Of note, there was no evidence that the relationship between childcare attendance and egg allergy differed by number of siblings (OR for egg allergy among children without siblings who attended childcare: 0.95; 95% CI, 0.71, 1.26), or that the relationship between mode of delivery and egg allergy differed by maternal history of allergy (OR for egg allergy among children born by caesarean section to mothers with a history of allergy: 0.91; 95% CI, 0.68; 1.22).

Discussion

This is the first population-based study to examine the influence of a wide range of environmental and demographic factors on challenge-confirmed egg allergy. In addition to our previous finding that timing of introduction of egg is strongly associated with infant egg allergy (13), we have now shown that infants with siblings, particularly young siblings, and infants with a pet dog inside the home, are less likely to be egg allergic at 1 year of age. Interestingly, infants with parents born in East Asia were more likely to be egg allergic compared with infants of Australian-born parents. We have previously reported that there was no evidence of an association between maternal consumption of egg and egg allergy in this cohort; thus, this factor was not included in this analysis (13).

The strengths of this study are the large sample size, population-based sampling frame and determination of egg allergy status using the gold standard of oral food challenge. The HealthNuts study was specifically designed as an infant cohort initially sampled at 12 months of age. Although this study design has some limitations related to the retrospective collection of exposure data, this design was chosen specifically to avoid some of the potential limitations of conducting birth cohort studies in relation to investigating risk factors for food allergy. Inclusion of infants from birth (or earlier) in an allergy study can lead to changes in easily modifiable behaviour such as infant feeding or maternal diet as participants in an allergy cohort may seek to become more aware and comply with the current recommended practices. To reduce the potential for recall bias, data were obtained prior to providing the results of skin prick testing or oral food challenges and recall error regarding number of siblings, infant attendance of childcare, current pet ownership and parents' country of birth is unlikely. Recall error may have occurred, but it is a relatively short period to have had to recall over, and recall error would result in nondifferential misclassification and bias towards null. For example, it is possible that the lack of association between antibiotic exposure and egg allergy in this study is attributed to recall error regarding antibiotic use by infants over a 12-month period.

Our finding of an inverse association between number of older siblings and egg allergy risk is consistent with one case-control study of children presenting to an allergy clinic (23). Dioun et al. reported that first-born children (with no older siblings) were over-represented among food-allergic cases ($n = 58$) compared with controls ($n = 96$) (OR, 2.22; 95% CI, 1.06–4.66). Our results confirm and extend this finding as we noted a stronger association between having siblings under the age of 6 years and egg allergy compared with siblings 6 years and older. Intra-household effects may be stronger before the age of regular school attendance (22), which in Victoria is required by 6 years of age.

Our study is the first large population-based study to examine the association between pet exposure and challenge-confirmed food allergy. One previous study involving 312 infants (15 with food allergy), reported no effect of cat or dog exposure on food allergy; however, the study would have

been underpowered to detect an association of the magnitude we describe here (24).

In contrast to the results of one previous population-based study (25), our findings do not support an association between caesarean section delivery and subsequent egg allergy. Eggesbo et al. reported no association between mode of delivery and egg allergy at the age of 2.5 years when considering the entire study cohort; however, there was modest evidence of an increase in egg allergy among children of allergic mothers delivered by caesarean section ($P = 0.08$). We found no evidence that children of allergic mothers delivered by caesarean section were at increased risk of egg allergy. Our finding is consistent with one other study that examined electronic medical records for 8953 children age 3–10 years, reporting no association between caesarean section delivery and any food allergy (26). Recent systematic reviews suggested that delivery by caesarean section is associated with an increased risk of other allergic diseases (asthma and allergic rhinitis) (27).

Our finding that preterm infants were less likely to be egg allergic is consistent with two recent studies which have reported that infants born preterm have a decreased risk of atopic sensitisation (23) and allergic rhinitis (28) later in life. Reasons for this association may include differences in the type and timing of transplacental exposure to allergens, pathogens or gastrointestinal flora (23, 28).

The strongest risk factor for egg allergy in this cohort was having one or more parents born in East Asia. Interestingly, parents born in East Asia were less likely to report a history of allergic disease themselves, while their infants are at increased risk of egg allergy and eczema (Martin et al., manuscript in preparation). This is consistent with the recent finding that US-born children of immigrants were at highest risk of food sensitisation, while those born and raised outside of the United States have the lowest risk (14). This could potentially be explained by a gene-environment interaction, whereby immigrants have particular genetic polymorphisms that protect against intestinal parasite infection but predispose to allergy risk when growing up in a pathogen-poor environment (14). This hypothesis is consistent with our finding that having a parent born in Europe did not increase the risk of infant egg allergy.

There is evidence that children with siblings have a greater incidence of infections, including upper and lower respiratory tract infections, otitis media and *Helicobacter pylori* infection (30–33). We speculate that the increased exposure to microbial stimulation resulting from contact with other children could aid the switch from a Th2-dominant immune response present *in utero* and associated with allergic disease to a Th1-dominant immune response seen in adults and associated with normal immune functioning, as has been proposed previously (34). However, a protective effect of early life infections is not consistent with our observation that childcare attendance was not associated with egg allergy, as an association between childcare attendance and increased symptomatic infections has also been well established (30). A recent study suggested that exposure to siblings might have a protective effect independent of any increase in symptomatic infections

Table 2 Multiple logistic regression of factors associated with egg allergy in infants (*N* = 4359)*

	Unadjusted		Adjusted†	
	OR (95% CI)	<i>P</i>	OR (95% CI)	<i>P</i>
Female gender	0.79 (0.65, 0.96)	0.018	0.81 (0.65, 1.00)	0.052
Preterm delivery	0.54 (0.32, 0.91)	0.021	0.52 (0.30, 0.92)	0.025
Number of siblings				
None	1.0		1.0	
One	0.74 (0.60, 0.93)		0.72 (0.57, 0.92)	
Two	0.62 (0.44, 0.86)		0.56 (0.38, 0.81)	
Three or more	0.32 (0.15, 0.65)	<i>P</i> trend:	0.31 (0.14, 0.68)	<i>P</i> trend:
Per sibling	0.75 (0.66, 0.85)	<0.001	0.72 (0.62, 0.83)	<0.001
Cat ownership				
No cat	1.0		1.0	
Cat outside only	0.79 (0.45, 1.41)	0.43	0.93 (0.49, 1.77)	0.83
Cat allowed inside	0.62 (0.45, 0.85)	0.004	0.75 (0.52, 1.09)	0.13
Dog ownership‡				
No dog	1.0		1.0	
Dog outside only	0.77 (0.55, 1.08)	0.13	1.09 (0.75, 1.57)	0.66
Dog allowed inside	0.55 (0.41, 0.73)	<0.001	0.72 (0.52, 0.99)	0.043
Age at first introduction of egg				
4–6 months	1.0		1.0	
7–9 months	1.11 (0.84, 1.46)		1.03 (0.77, 1.39)	
10–12 months	1.30 (0.98, 1.73)	<i>P</i> trend	1.28 (0.95, 1.74)	<i>P</i> trend
>12 months	4.87 (3.30, 7.18)	<0.001	4.36 (2.84, 6.67)	<0.001
Immediate family (parent/s or sibling/s) history of allergy	1.58 (1.26, 1.99)	<0.001	1.82 (1.40, 2.36)	<0.001
Parent's country of birth				
Both parents born in Australia	1.0		1.0	
One† or both born in East Asia	3.30 (2.53, 4.30)	<0.001	3.30 (2.45, 4.45)	<0.001
One† or both born in Europe	1.31 (0.96, 1.81)	0.092	1.25 (0.88, 1.77)	0.21
Other	1.29 (0.99, 1.70)	0.060	1.33 (0.98, 1.81)	0.072
Maternal smoking during pregnancy	0.35 (0.17, 0.72)	0.004	0.56 (0.26, 1.22)	0.14
Socio-economic status				
Quintile 1 (most disadvantaged)	1.0		1.0	
Quintile 2	1.52 (1.10, 2.09)		1.31 (0.92, 1.87)	
Quintile 3	1.23 (0.89, 1.71)		0.98 (0.67, 1.42)	
Quintile 4	1.44 (1.04, 1.98)	<i>P</i> trend	1.25 (0.87, 1.80)	<i>P</i> trend
Quintile 5 (least disadvantaged)	1.51 (1.09, 2.08)	0.044	1.23 (0.85, 1.78)	0.47

*577 infants had missing data on one or more covariates so were excluded from this analysis.

†One parent born in East Asia/Europe, second parent born in Australia.

‡The association between dog ownership and infant egg allergy was additionally adjusted for infant history of eczema, which emerged as an important confounder of this association.

(11). It is also possible that an increase in maternal exposure to microbial stimulation during pregnancy resulting from contact with young children is responsible for the observed decrease in egg allergy in offspring.

There is some evidence from previous studies that the protective effect of childcare attendance on other allergic outcomes may be greater among those with no older siblings (35). However, we found no evidence of an interaction between number of siblings and childcare attendance in determining the risk of egg allergy in infants.

The apparent protective effect of dog exposure on egg allergy observed in our study might be due to increased exposure to microbial products resulting from contact with pets.

Pet ownership increases exposure to endotoxin – a component of the cell wall of Gram-negative bacteria – as well as potentially increasing exposure to a number of intestinal helminths (36, 37). Some studies have reported an association between high-endotoxin environments and a reduced risk of allergy (38). However, a recent study indicated that endotoxin and pets might have separate protective effects (39), suggesting that other microbial exposures associated with pet keeping could be responsible for the observed decrease in allergy risk.

This study provides the first investigation of the relationship between environmental and demographic factors previously hypothesised to play a role in the development of

food allergy and risk of challenge-confirmed egg allergy in infants. Both contact with pets and having older siblings were associated with a decreased risk of infant egg allergy, while having a parent born in East Asia was associated with an increased risk. These findings may provide further support for a role of the hygiene hypothesis, in combination with genetic factors, in the development of allergic disease.

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Author contribution

J. Koplin, K. Allen, L. Gurrin, and S. Dharmage developed the analysis plan. J. Koplin conducted the data analysis and

produced draft manuscript. K. Allen, A.-L. Ponsonby, L. Gurrin, M. Tang, A. Lowe, M. Wake, D. Hill and S. Dharmage conceived the HealthNuts study and gained funding. N. Osborne, P. Martin, M. Robinson and the HealthNuts Investigators contributed to data collection. All authors reviewed and refined the manuscript and approved the final version.

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Conflict of interest

The authors have no conflict of interest to declare.

Supporting Information

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

Data S1. Methods.

Figure S1. Sensitivity analysis of risk factors for egg allergy.

Table S1. Questions asked of parent/guardians at recruitment relating to environmental and demographic factors.

Table S2. Classification of parents' region of birth.

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Supplementary material

Methods

Socioeconomic status was assigned to each participant based on their home postcode using SEIFA (Socio-Economic Indexes For Areas) measures derived from the 2006 Australian census, which assess relative socio-economic advantage and disadvantage, economic resources (income, assets and expenditure) and educational and occupational characteristics (1). SEIFA scores were classified into quintiles for all analyses.

Sensitivity analysis

A sensitivity analysis was performed to examine the likely effect of missing data on egg allergy status and further sensitivity analyses were performed to test the robustness of our results when using different definitions for egg allergy. For infants who did not attend OFC, those with a skin prick test wheal size of $\geq 5\text{mm}$ to egg (2) and/or a history of reaction to egg in the context of a positive SPT were classified as “likely egg allergic” (n=58). Infants with a reported history of tolerating at least $\frac{1}{2}$ of a semi-cooked egg (soft-boiled or scrambled) at home and/or a SPT wheal size $<2\text{mm}$ were classified as “likely egg tolerant” (n=79). Using this classification, we reanalyzed the data including infants with missing data on egg allergy status by assuming that those classified “likely egg allergic” or “likely egg tolerant” were allergic or tolerant respectively. Those infants who could not be classified into either of these categories were excluded from the analysis.

Further sensitivity analyses were performed to test the robustness of our results when using different definitions for egg allergy as follows: 1) Infants with a positive oral food challenge to egg and evidence of egg sensitisation (primary outcome used throughout this paper), N=453; 2) All infants with a positive oral food challenge to egg (regardless of sensitisation

status), N=479; 3) Infants with a positive oral food challenge to egg and an egg SPT wheal size ≥ 3 mm greater than the negative control (N=328); 4) Infants with any parent-reported reaction to egg in the first year of life (N=316).

The sensitivity analysis showed that most of the associations remained stable regardless of the skin prick test wheal size cut-off employed to define IgE-mediated egg allergy (Figure S1). For most variables, using parent-reported egg allergy as the outcome measure produced odds ratios which were closer to 1, which is not surprising as parent-report is likely to provide an inaccurate measure of true egg allergy. An exception was for socioeconomic status, where parents from the highest SEIFA quintile (least disadvantaged) were more likely to report egg allergy in their child.

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Table S1: Questions asked of parent/guardians at recruitment relating to environmental and demographic factors

	Question asked in parent/guardian administered questionnaire:
Mode of delivery	How was your child born? Tick boxes for vaginal or caesarean section
Pet ownership	Do you have pets at home? Options: -Cat: inside / outside / both -Dog: inside / outside / both -Bird: inside / outside / both -Other pet (describe): inside / outside / both
Siblings	Does your 12 month old have other brothers and sisters? -Tick box for “no” or “yes”. -Boxes provided for date of birth for up to 5 siblings
Number of household residents	The following people live with my child in our house (for at least half the week). The child’s ... - Father - Mother - Siblings (as described above) - Other relatives (describe) - Other people (describe)
Child care attendance	Does your child attend childcare / daycare? - Tick box for “no” or “yes” - Number of days per week - Number of hours per session At what age did they begin (months old)?
Use of antibiotics	Has your child ever had antibiotics? - Options: “no”, “yes” or “not sure” - Age (months) - Reason for antibiotics - Type of antibiotic (if known) - If more than one course of antibiotic, how many?
Family history of allergy	‘Does anyone in the family suffer from...?’ - ‘Asthma’ - ‘Eczema’ - ‘Hay fever’ - ‘Food allergy (please specify)’ Separate tick boxes provided for mother, father and each sibling.
Maternal smoking during pregnancy	Did the mother smoke in pregnancy?
Current smoking by any household member	Does anyone smoke inside the home? Who? - Number of cigarettes per day

	Does anyone smoke outside the home (e.g. in the garden)? Who? - Number of cigarettes per day
Mother's and Father's country of birth	In what country was the child's mother born? In what country was the child's father born?
Gestational age at delivery	At how many weeks gestation did you deliver this child?

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.
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

Figure S1: Sensitivity analysis of risk factors for egg allergy. Adjusted odds ratios (OR) and 95% confidence intervals for the risk factors for egg allergy as per Table 2 are shown. Egg allergy was defined as: 1) Infants with a positive oral food challenge to egg and evidence of egg sensitisation (results from Table 2); 2) All infants with a positive oral food challenge to egg; 3) Infants with a positive oral food challenge to egg and an egg SPT wheal size $\geq 3\text{mm}$; 4) Infants with a positive oral food challenge to egg or a skin prick test wheal size $\geq 5\text{mm}$ to egg or a history of reaction to egg in the context of a positive SPT; 5) Infants with any parent-reported reaction to egg in the first year of life.

