Food allergy is an important risk factor for childhood asthma, irrespective of whether it resolves

AUTHORS: Evelien M Vermeulen[1]*, BSc, Jennifer J Koplin[1,2]*, PhD, Shyamali C Dharmage[1,2], MBBS, MSc, MD, PhD, Lyle C Gurrin[1,2], PhD, Rachel L Peters[1], PhD, Vicki McWilliam[1,2,3], BSc, MND, Anne-Louise Ponsonby[1], MBBS, FAFPHM, FRACP, PhD, Terence Dwyer[1,4], PhD, Adrian J Lowe[1,2], PhD, Mimi LK Tang[1,2,3], MBBS, PhD, FRACP, FRCPA, FAAAAI, Katrina Allen[1,2,3,5], MBBS, BMedSC, FRACP, FAAAAI, PhD for the HealthNuts investigators

*These authors contributed equally to this manuscript

Affiliations:

[1] Murdoch Childrens Research Institute, Parkville, Vic, Australia

[2] Centre for Epidemiology and Biostatistics, University of Melbourne, Parkville, Vic, Australia

[3] Department of Allergy and Immunology, Royal Children's Hospital, Parkville, Vic, Australia

[4] George Institute for Global Health, Dept. of Obstetrics and Gynaecology, University of Oxford, Oxford, UK

[5] Institute of Inflammation and Repair, University of Manchester, Manchester, UK

The HealthNuts study investigators are Melissa Wake, Melanie Matheson, Colin Robertson and David Hill.

CORRESPONDING AUTHOR:

Professor Katie J. Allen

Murdoch Childrens Research Institute

Royal Children's Hospital, Flemington Rd,

Parkville 3052, Victoria, Australia

Email: katrina.allen@mcri.edu.au

Phone: +613 9936 6585

27

28 **WORD COUNT:** 3,394

Abstract

Background: The risk of developing asthma in those with early food allergy is unknown, particularly when early life food allergy has resolved.

Objective: To understand whether challenge-proven food allergy in infancy increases the risk of asthma at age 4, using data from a population-based cohort.

Methods: 5,276 12-month-old infants were recruited using a population-based sampling frame. Infants underwent skin prick test to egg, peanut and sesame and those with a detectable skin prick test had oral food challenges. At age 4 years food challenges were repeated to determine persistence or resolution of food allergy. The association between food allergy and doctor diagnosed asthma was examined using binomial regression in 2,789 participants.

Results: Children with food allergy at age one year had an increased risk of asthma (one food allergy: RR 1.69, 95%CI 1.29-2.21; two or more food allergies: RR 2.76, 95%CI 1.94-3.92). The risk of asthma was highest in children with food allergy and co-existent eczema in infancy (RR 2.87, 95%CI 2.22-.70). Transient and persistent food allergy were both associated with an increased risk of asthma (transient egg allergy: RR 1.92, 95%CI 1.46-2.51; persistent egg allergy: RR 2.60, 95%CI 1.76-3.85).

Conclusion: Asthma at age 4 years is twice as common in those with challenge-proven food allergy at age 1 year, irrespective of whether the food allergy subsequently resolves. Children with two or more food allergies and those with co-existent eczema were around three times as likely to develop asthma compared to those with no food allergies.

Keywords: food allergy; asthma; eczema; wheeze; oral food challenge; infants

Abbreviations:

SPT: Skin prick test

OFC: Oral food challenge

RR: Relative risk

55 CI: Confidence interval

56 ISAAC: International Study of Asthma and Allergies in Childhood

57 Funding: This work was supported by funding from the National Health & Medical Research Council
58 (NHMRC) of Australia, Ilhan Food Allergy Foundation, AnaphylaxiStop, the Charles and Sylvia Viertel
59 Medical Research Foundation, the Victorian Government's Operational Infrastructure Support
60 Program and the NHMRC Centre for Food and Allergy Research. KA, LG, JK, AL, A-LP and SD hold
61 NHMRC awards.

What is already known about this topic? Allergic sensitization, including food sensitization, is positively associated with asthma or respiratory symptoms, however the role of clinical food allergy in this relationship has not been explored at the population level.

What does this article add to our knowledge? This article provides evidence that oral food challenge confirmed food allergy in infancy is associated with an increased risk of asthma at the age of four irrespective of whether the early food allergy resolves. The risk is higher for those with multiple food allergies and those with co-existent eczema.

How does this study impact current management guidelines? This data can be used by clinicians to inform families of children with food allergies about their child's risk of developing asthma in early childhood, and to identify children who may need closer follow up and monitoring of their respiratory health. Understanding whether the prevention of early life food allergy prevents the development of later asthma will be an important challenge for the future.

62

Introduction

Childhood food allergy appears to be becoming increasingly common worldwide. (1, 2) Food allergy mostly presents for the first time in infancy but there is currently little high-quality data available for clinicians to inform parents of food allergic infants about their child's risk of later allergic outcomes, particularly asthma.

There is indirect evidence that individuals with food allergy in infancy might be at increased risk of asthma in later life. Small case-control studies of food allergic infants suggest a relatively high rate of asthma in later life (3, 4) and food allergy and asthma often co-exist in older children (5, 6). A recent systematic review and meta-analysis of thirteen birth cohort studies reported that early food sensitization is associated with subsequent asthma in childhood.(7) However, no previous population-based studies have determined whether children with clinical food allergy, defined by positive oral food challenges, in early life have a greater risk of developing asthma than those with asymptomatic food sensitisation. Eczema in infancy is also associated with an increased risk of asthma, and early onset eczema is associated with increased risk for food allergy.(8-10) The prospective role of challenge confirmed food allergy, separate from and in combination with eczema, has to our knowledge never been explored in a longitudinal population-based study.

We recently reported that over ten percent of 1-year-old infants born between 2006 and 2010 in Melbourne, Australia had a challenge-proven IgE-mediated food allergy, with the majority of this burden driven by a high prevalence of egg allergy.(11) Even though egg allergy often resolves in early childhood, egg allergic infants might be at increased risk of other allergic conditions throughout childhood.

The aim of this longitudinal study was to investigate the relationship between the presence and number of food allergies at 1 year of age and asthma at age 4 years. We also assessed if these

associations were influenced by persistence versus resolution of food allergy, early life wheeze and eczema.

Methods

HealthNuts study

The HealthNuts study is a longitudinal population-based cohort study of allergic disease in Melbourne, Australia. Recruitment has been described in more detail previously.(12) Concisely, 5,276 infants between 11 and 15 months of age were recruited from immunization clinics around Melbourne with a 74% participation rate. Participants underwent a skin prick test (SPT) at recruitment to egg, peanut, sesame and either cow's milk or shrimp and were examined for eczema whilst the parents completed a questionnaire. SPTs were administered with a single-tine lancet (Stallergenes, Antony, France) on the child's back using allergen extracts (ALK-Abello, Madrid, Spain) along with a positive control (10 mg/mL histamine) and a negative control (saline). Wheal size was measured after 15 minutes and calculated as the average of the longest diameter and the diameter perpendicular to it and then subtracting the negative control SPT diameter. If a participant had a reaction to the skin prick test (a wheal ≥1 mm) to egg, peanut or sesame, regardless of the wheal size, the child was invited for an oral food challenge (OFC) to that food at the Royal Children's Hospital in Melbourne.(13)

When the children turned 4 years of age all parents were asked to complete a second questionnaire about their child's health and allergies. Questions on key allergic outcomes (asthma, eczema and allergic rhinitis) included those from the International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire.(14) If parents did not return the questionnaire a reminder was sent and if after the final reminder phone call parents had not returned the questionnaire, they were asked to complete a short 5-minute telephone questionnaire which captured essential information on their child's current allergy status. Children with a food allergy at age 1 were asked to attend an assessment at the hospital at age 4 years, which included a skin prick test and oral food challenge to test for persistence or resolution of their food allergy.(15)

Oral food challenges:

OFCs were conducted as previously described, with challenge staff blinded to SPT wheal size and previous clinical history.(13) Criteria for a positive OFC were more than 3 non-contact urticarial reactions lasting more than 5 minutes, angioedema, vomiting or anaphylaxis, within 2 hours of the last challenge dose. On discharge those with a negative challenge were administered a daily single serving of the challenge food at home for 7 days to capture any subsequent acute allergic reactions.

The food challenge result was deemed negative if the child tolerated the top dose of the challenge food and did not report a subsequent reaction in the following week. Food challenges were deemed inconclusive and the parents were offered a repeat challenge if the child refused to ingest the challenge food at the clinic or if the parent reported a subsequent reaction that did not meet the positive challenge criteria yet led the parent to remove the food from the child's diet. In addition, positive OFC results in children without any evidence of IgE sensitization to the allergen were considered inconclusive, as we could not be certain that the reaction was due to an IgE-mediated mechanism.

Definitions

Food sensitized age 1: a wheal of two millimetres or more on any of the skin prick tested foods.

Sensitized tolerant: a wheal of two millimetres or more to egg, peanut or sesame, but a negative oral food challenge to this food.

Food allergy age 1: a positive oral food challenge (or recent reaction consistent with OFC stopping criteria) to egg, peanut or sesame, in infants with evidence of sensitization to that food.

Persistent egg allergy: A positive oral food challenge (or recent reaction consistent with OFC stopping criteria) at both 1 and 4 years of age, as described previously.(16)

Transient/resolved egg allergy: A positive oral food challenge at the age of 1 year, followed by a negative oral food challenge at 4 years of age, or a history of ingesting egg without reaction, as described previously.(16)

Asthma (primary analysis): a parental report of doctor-diagnosed asthma on the age 4 survey.

Asthma (sensitivity analysis): To ensure our findings were robust to different definitions of the asthma outcome, we also tested for associations with the following asthma outcomes: (1) Parent report of asthma ever (age 4 survey); (2) Current asthma at age 4 years (parent report of asthma diagnosis, with either wheezing episodes or asthma medication use in the past 12 months); (3) Parent report of wheeze in the past 12 months (age 4 survey), with separate analyses conducted for "any wheeze" and "4 or more episodes of wheeze" in the past 12 months.

Eczema (primary analysis): A parental report of eczema diagnosis in the first year of life.

Eczema (sensitivity analysis): To capture potential cases of undiagnosed eczema, analyses were repeated using a broad definition of eczema which included infants with any of the following in the first year of life: eczema diagnosis; parent report of itchy rash (other than nappy/diaper rash) which was treated with topical steroids; and nurse-observed eczema present at recruitment.

Infant wheeze: a parental report of an episode of wheeze ever in the first year of life.

Statistical Analysis

The association between food allergy and asthma was modelled using binomial regression (a generalised linear model with a logarithm link function) from which estimates of relative risk ratios (RR) and the corresponding 95% confidence intervals were generated. We adjusted for the following variables that could potentially confound the association between the primary exposure (food allergy) and the outcome (asthma) based on previous published studies: sex, socioeconomic status and having a parent or sibling with asthma or other allergies. Parents' country of birth (at least one parent from East Asia) was included as a confounder as a result of our own work.(18) We also considered the following additional potential confounders: presence of a pet dog in the household, having any siblings, maternal smoking during pregnancy, birth weight, duration of exclusive breastfeeding (<=3 months vs >3 months) and season of birth (winter vs other).(19, 20) Variables

from this list whose inclusion in the binomial regression model resulted in a change in the estimated relative risks for the association between food allergy and asthma of more than 10% were included in the final model from which results were derived.

The primary aim of this analysis was to determine the relative risk of asthma in children with and without food allergy in infancy. We also aimed to investigate the longitudinal association between food allergy at age 1 year and the subsequent development of asthma, i.e. to assess newly incident disease after age 1. We therefore repeated all analyses after excluding children with either wheezing in the first year of life (which can be an early symptom of asthma (17)), as well as participants who received an asthma diagnosis before 1 year of age.

To investigate the role of early life eczema in the association between food allergy and asthma, we created a variable which categorised infants into 4 groups: no eczema and no food allergy; eczema alone; food allergy alone; eczema and food allergy, and calculated the relative risk of asthma for each group compared to the baseline of no eczema and no food allergy. We also performed an interaction test to determine whether the association between food allergy and asthma was modified by the presence or absence of eczema. Binomial regression models with and without interactions were compared using the quasi-likelihood ratio test.

To further investigate the role of early life wheeze in the association between food allergy and asthma, we performed an interaction test to determine whether the association between food allergy and asthma was modified by the presence or absence of wheeze in the first year of life, with interaction tests performed as described above.

Sensitivity analyses for missing data

The primary analysis included only individuals with data available from the full questionnaire, which specifically asked about history of asthma and wheeze and whether asthma had been diagnosed by a doctor. The short questionnaire collected information on asthma/wheeze using a single question about whether the child ever had either asthma or wheezing or whistling in the chest. In order to include a larger proportion of the cohort in the analysis, we performed a sensitivity analysis using information from the short questionnaire along with the full questionnaire data.

To further explore the potential impact of missing data, we adjusted for differences in demographic characteristics or other risk factors between participants with and without missing data at age 4 years using the inverse probability weighting method described by Little and Rubin (see online repository for details).(21)

All analyses were performed using Stata 14.1 for Windows (StataCorp LP, College Station, TX, USA).

Ethics

Ethical approval was obtained from the Office for Children HREC (ref. no. CDF/07/492), Department of Human Services HREC (ref. no. 10/07) and Royal Children's Hospital HREC (ref. no.27047 and 32294). All parents/guardians provided written informed consent.

Results

Participation

The HealthNuts cohort included 5,276 participants at 1 year of age, with 81% of these followed up at age 4 years (Figure 1). The primary analysis included 2,789 participants who completed the full questionnaire and had complete data on exposure, outcome and confounders. Of these, 422 (15%) had a history of wheeze or asthma in the first year of life, and were therefore excluded from secondary analyses. An additional 1,012 infants had asthma information available from the short questionnaire and were included in the sensitivity analysis.

Sensitization, food allergy and asthma

Both asymptomatic food sensitisation (sensitised tolerant) and true food allergy at age 1 year were associated with an increased risk of asthma at age 4 years (Table I). Participants with a food allergy were twice as likely as non-sensitized participants to develop asthma (adjusted RR 2.13, 95%CI 1.71, 2.64). The risk of asthma was higher for children with a true food allergy compared to children with asymptomatic food sensitization, although the difference did not reach statistical significance ($p=0.37$).

When investigating only newly incident disease which started after age 1 year, the risk of asthma was 2.5-fold higher for children with food allergy and 2-fold higher for children with asymptomatic food sensitisation (Table I).

Results were similar irrespective of how asthma was defined (Online Repository Table E1). Results were also consistent in the sensitivity analysis which included participants who completed only the short questionnaire, although the association was slightly attenuated, possibly due to the less strict definition of asthma in the short questionnaire.

Number and type of food allergies at age 1 year and risk of asthma

The risk of asthma at age 4 years increased with an increasing number of food allergies at age 1 year (Table II). Children with two or more food allergies had a significantly higher risk of asthma compared to those with only one food allergy (p=0.016).

Egg and peanut allergy were the most common food allergies in this cohort at age 1 year. Children without food allergy were compared with those who have only an egg allergy, only a peanut allergy and with those who have both egg and peanut allergy (Table II). No separate group was made for sesame allergy in this analysis, because of the small number of cases (n=14). Egg allergy alone was associated with a higher risk of asthma (RR 2.00, 95%CI 1.52-2.59), while peanut allergy alone was not associated with an increased risk, possibly due to a small number of children in this group. Children with both peanut and egg allergy had the highest risk of asthma (RR 2.88, 95%-CI 1.98, 4.17).

Persistent and transient egg allergy

Table III shows the risk of asthma in children with persistent egg allergy at age 4 years and those with transient egg allergy which has resolved by 4 years of age. Both persistent and transient egg allergy were associated with an increased risk of asthma compared with never having an egg allergy, and there was no evidence of a difference in risk according to whether or not the egg allergy resolved by age 4 years (p=0.18).

We did not examine the impact of transient versus persistent peanut allergy since relatively few (n=22) infants resolved their peanut allergy by 4 years of age.

Relationship between eczema and food allergy and risk of asthma

Table IV shows the relative risk for food allergy and eczema separately and combined (both risk factors present). Both eczema alone and food allergy alone increased the risk of asthma at age 4

years. There appeared to be an additive effect for eczema and food allergy, since the risk of asthma was higher for children with both eczema and food allergy compared to those with eczema alone ($p<0.001$) and those with food allergy alone ($p=0.018$).

Results were similar when we used a broad definition of eczema which also captured potential undiagnosed cases of eczema (Online Repository Table E2), although the association with food allergy alone was attenuated in this analysis.

There was no evidence that the association between food allergy and asthma differed for children with and without eczema (Online Repository Table E3; p interaction=0.98).

Role of early life wheeze in the association between food allergy and asthma

Infants with a history of wheeze in the first year of life were more likely to be diagnosed with asthma at age 4 years compared to those without a history of wheeze (11.2% vs 27.4%, $p<0.001$). There was no evidence of an association between wheeze in the first year of life and food allergy ($p=0.99$), and the association between food allergy and asthma diagnosis was similar for infants with and without a history of wheeze (Online Repository Table E3; p interaction = 0.16).

Discussion

This is the first population based cohort study using challenge-proven outcomes to assess the role of infantile food allergy in the subsequent development of childhood asthma. We found that both asymptomatic food sensitisation and food allergy in infancy are associated with an increased risk of asthma by age 4 years. The risk of asthma was higher for children with two or more food allergies in infancy than for those with a single food allergy. Both transient and persistent food allergy were associated with a similar magnitude of increase in risk of asthma. Having both infantile eczema and food allergy almost tripled the risk of having asthma at age 4 compared to no eczema and no food allergy.

Strengths of this study include the cohort size and its population-based, prospective study design. Rates of participation in the study were high (74%) and participants were broadly representative of the general population (8). Another strength is that food allergies were confirmed by an oral food challenge for all infants with a positive SPT, regardless of wheal size, and therefore we were able to distinguish between food sensitised tolerant and food sensitised allergic children – something that previous studies have been unable to do.

Limitations included missing information on asthma diagnosis at age 4 years for participants who did not complete the full questionnaire, however a sensitivity analysis using asthma symptoms as an outcome from short questionnaire data shows the same trend as found for asthma diagnosis. There were some differences in characteristics of children who were lost to follow up compared with those included in the analysis, which may limit the generalisability of our findings, however we found similar results when we included sampling weights in our models to account for differences in the distribution of these factors among participants compared with the whole cohort.

Asthma status was determined by parent report of a doctor diagnosis at age 4 years. Validated questionnaires and objective testing for asthma are only available for children over five years of age. Although the accuracy of asthma diagnosis in children younger than 5 years is debated, we found the same results using multiple definitions of asthma and wheezing symptoms, providing further support for our findings. We will confirm these associations in follow-ups of this cohort at later ages when the diagnosis of asthma is more definitive.

This study showed that food sensitization alone, without a positive oral food challenge, does increase the risk of asthma, but for food allergic children (particularly those with multiple food allergies) the risk is even higher. These findings suggest that studies so far, using food sensitization as an indicator for food allergy (19, 22, 23), may underestimate the asthma risk.

Egg allergy was found to be a strong risk factor for asthma in children, and the risk was similar for both transient and persistent egg allergy. This finding is important for interpreting the results of previous cross-sectional research into food allergy and asthma in older children, since this is likely to have missed children who have outgrown their allergy.(19, 20, 22) Peanut allergy occurred most often in children who also had egg allergy, and there were insufficient cases to reliably analyse the effect for peanut allergy alone, however the risk of asthma was greatest in children who had more than one food allergy.

There is limited previous population-based research into the relationship between food allergy and asthma using oral food challenges. Most studies focus only on food sensitization or skin prick test, and some also used report of symptoms after ingestion to define food allergy. There is only one previous population-based prospective birth-cohort of 1,218 newborns in the UK, of which 29 (2.4%) had symptoms of egg allergy (not confirmed by challenges) by 2 years of age. Egg allergy was associated with an increased risk of any respiratory disease (asthma or rhinitis) at age 4 years (OR

5.0, 95% CI 1.1-22.3), although they found no significant relationship with asthma alone, possibly due to lack of statistical power.(23) Various models for predicting later childhood asthma have been developed for preschool children. Some of these consider presence or absence of specific IgE to foods, however consideration of clinical food allergy status in these models is rare (24).

Our study adds to existing knowledge regarding the atopic march. Knowing that having food allergy and eczema increases the chance of subsequent asthma, makes it possible to identify children at highest risk, who might benefit from additional screening for asthma to ensure optimal early management.

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 SPTs. Finally we thank the HealthNuts study research staff: Nicholas Osborne, Megan Mathers, Dean Tey, Marnie Robinson, Giovanni Zurzolo, Leone Thiele, Helen Czech, Deborah Anderson, Carley Garner and John Molloy.

FUNDING: This work was supported by funding from the National Health & Medical Research Council (NHMRC) of Australia, Ilhan Food Allergy Foundation, AnaphylaxiStop, the Charles and Sylvia Viertel Medical Research Foundation, the Victorian Government's Operational Infrastructure Support Program and the NHMRC Centre for Food and Allergy Research.

References

1. Koplin JJ, Mills EN, Allen KJ. Epidemiology of food allergy and food-induced anaphylaxis: is there really a Western world epidemic? Curr Opin Allergy Clin Immunol. 2015;15(5):409-16.

2. Prescott S, Allen KJ. Food allergy: riding the second wave of the allergy epidemic. Pediatr Allergy Immunol. 2011;22(2):155-60.

3. Saarinen KM, Pelkonen AS, Makela MJ, Savilahti E. Clinical course and prognosis of cow's milk allergy are dependent on milk-specific IgE status. J Allergy Clin Immunol. 2005;116(4):869-75.

4. Priftis KN, Mermiri D, Papadopoulou A, Papadopoulos M, Fretzayas A, Lagona E. Asthma symptoms and bronchial reactivity in school children sensitized to food allergens in infancy. J Asthma. 2008;45(7):590-5.

5. Schroeder A, Kumar R, Pongracic JA, Sullivan CL, Caruso DM, Costello J, et al. Food allergy is associated with an increased risk of asthma. Clin Exp Allergy. 2009;39(2):261-70.

6. Foong RX, du Toit G, Fox AT. Asthma, Food Allergy, and how they relate to each other. Front Pediatr. 2017;9(5):89.

7. Alduraywish SA, Lodge CJ, Campbell B, Allen KJ, Erbas B, Lowe AJ, et al. The march from early life food sensitization to allergic disease: a systematic review and meta-analyses of birth cohort studies. Allergy. 2016;71(1):77-89.

8. Martin PE, Eckert JK, Koplin JJ, Lowe AJ, Gurrin LC, Dharmage SC, et al. Which infants with eczema are at risk of food allergy? Results from a population-based cohort. Clin Exp Allergy. 2015;45(1):255-64.

9. Ekback M, Tedner M, Devenney I, Oldaeus G, Norrman G, Stromberg L, et al. Severe eczema in infancy can predict asthma development. A prospective study to the age of 10 years. PLoS One. 2014;9(6):e99609.

10. Dharmage SC, Lowe AJ, Matheson MC, Burgess JA, Allen KJ, Abramson MJ. Atopic dermatitis and the atopic march revisited. Allergy. 2014;69(1):17-27.

11. Osborne NJ, Koplin JJ, Martin PE, Gurrin LC, Lowe AJ, Matheson MC, et al. Prevalence of challenge-proven IgE-mediated food allergy using population-based sampling and predetermined challenge criteria in infants. J Allergy Clin Immunol. 2011;127(3):668-7.

12. 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(10):1516-22.

13. Koplin JJ, Tang ML, Martin PE, Osborne NJ, Lowe AJ, Ponsonby AL, et al. Predetermined challenge eligibility and cessation criteria for oral food challenges in the HealthNuts population-based study of infants. J Allergy Clin Immunol. 2012;129(4):1145-7.

14. Asher MI, Keil U Fau - Anderson HR, Anderson Hr Fau - Beasley R, Beasley R Fau - Crane J, Crane J Fau - Martinez F, Martinez F Fau - Mitchell EA, et al. International Study of Asthma and Allergies in Childhood (ISAAC): rationale and methods. Eur Respir J. 1995;3:483-91.

15. 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(4):1161-71.

16. 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(1):145-53.

17. Martinez FD, Wright Al Fau - Taussig LM, Taussig Lm Fau - Holberg CJ, Holberg Cj Fau - Halonen M, Halonen M Fau - Morgan WJ, Morgan WJ. Asthma and wheezing in the first six years of life. The Group Health Medical Associates. N Engl J Med 1995;332(3):133-8.

18. 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(12):1639-47.

19. Schroeder A, Kumar R, Pongracic JA, Sullivan CL, Caruso DM, Costello J, et al. Food allergy is associated with an increased risk of asthma. Clin Exp Allergy. 2009;39(2):261-70.

20. Graif Y, German L, Livne I, Shohat T. Association of food allergy with asthma severity and atopic diseases in Jewish and Arab adolescents. Acta Paediatrica. 2012;101(10):1083-8.

21. Little RJ, Rubin DB. Statistical analysis with missing data: John Wiley & Sons; 2002.

22. Pénard-Morand C, Raherison C, Kopferschmitt C, Caillaud D, Lavaud F, Charpin D, et al. Prevalence of food allergy and its relationship to asthma and allergic rhinitis in schoolchildren. Allergy. 2005;60(9):1165-71.

23. Tariq SM, Matthews SM, Hakim EA, Arshad SH. Egg allergy in infancy predicts respiratory allergic disease by 4 years of age. Pediatr Allergy Immunol. 2000;11(3):162-7.

24. Smit HA, Pinart M, Antó JM, Keil T, Bousquet J, Carlsen KH, et al. Childhood asthma prediction models: a systematic review. Lancet Respir Med. 2015;3(12):973-84.

Figure legends:

Figure 1: Study participation and follow up at 4 years of age

Table I. Relationship between food sensitization and allergy at age 1 year and asthma at age 4 years.

	Total	Asthma (%)	Relative risk (95%-CI)*	p-value
All infants				
Not sensitized	2303	264 (11.5%)	1.0	-
Sensitized tolerant	68	13 (19.2%)	1.65 (1.00, 2.74)	0.052
Food allergic	368	88 (23.9%)	2.13 (1.71, 2.64)	<0.001
Excluding infants with wheeze or asthma in first year of life				
Not sensitized	1728	146 (8.5%)	1.0	
Sensitized tolerant	51	9 (17.7%)	2.02 (1.08, 3.78)	0.028
Food allergic	277	57 (20.6%)	2.51 (1.90, 3.31)	<0.001

*Adjusted for parents' country of birth, sex, socioeconomic status and family history of allergic disease.

Table II. Relationship between number and type of food allergy at age 1 year and asthma at age 4 years

	Total	Asthma (%)	Relative risk (95%-CI)*	p-value
All infants†				
Number of food allergies:				
One food	266	52 (19.6%)	1.69 (1.29, 2.21)	<0.001
Two or more foods	80	25 (31.3%)	2.76 (1.94, 3.92)	<0.001
Food allergy type:				
Egg allergy only	236	52 (22.0%)	2.00 (1.52, 2.59)	<0.001
Peanut allergy only	39	4 (10.3%)	0.91 (0.36, 2.35)	0.85
Egg and peanut allergy	71	22 (31.0%)	2.88 (1.98, 4.17)	<0.001
Excluding infants with wheeze or asthma in first year of life†				
Number of food allergies:				
One food	203	35 (17.2%)	1.99 (1.43, 2.78)	<0.001
Two or more foods	60	16 (26.7%)	3.01 (1.91, 4.75)	<0.001
Food allergy type:				
Egg allergy only	183	35 (19.1%)	2.41 (1.73, 3.37)	<0.001
Peanut allergy only	26	2 (7.7%)	0.91 (0.24, 3.45)	0.88
Egg and peanut allergy	55	15 (27.3%)	3.33 (2.08, 5.32)	<0.001

*Adjusted for parents' country of birth, sex, socioeconomic status and family history of allergic disease.

† The baseline group for all comparisons was infants with no food allergies

Table III. Relationship between persistent and transient egg allergy and asthma at age 4 years.

	Total	Asthma (%)	Relative risk (95%-CI)*	p-value
All infants				
Never been egg allergic	2521	296 (11.7%)	1.0	-
Transient egg allergy[†]	225	49 (21.8%)	1.92 (1.46, 2.51)	<0.001
Persistent egg allergy[‡]	66	19 (28.8%)	2.60 (1.76, 3.85)	<0.001
Excluding infants with wheeze or asthma in first year of life				
Never been egg allergic	1892	169 (8.9%)	1.0	
Transient egg allergy[†]	172	34 (19.8%)	2.29 (1.64, 3.19)	<0.001
Persistent egg allergy[‡]	52	11 (21.2%)	2.51 (1.47, 4.29)	0.001

*Adjusted for parents' country of birth, sex, socioeconomic status and family history of allergic disease.

[†] Transient egg allergy: A positive oral food challenge at the age of 1 year, followed by a negative oral food challenge at 4 years of age. A small number of participants who were eligible for but declined a food challenge at age 4 were assigned a probable tolerant status due to a negative SPT or parent-reported history of tolerance (ingestion of egg without reaction), as previously reported.(11) A subgroup of egg allergic infants were invited to participate in a sub-study which included OFC to test for early resolution of egg allergy at age 2 years,(12) and those with a negative food challenge were also categorised as transient egg allergy.

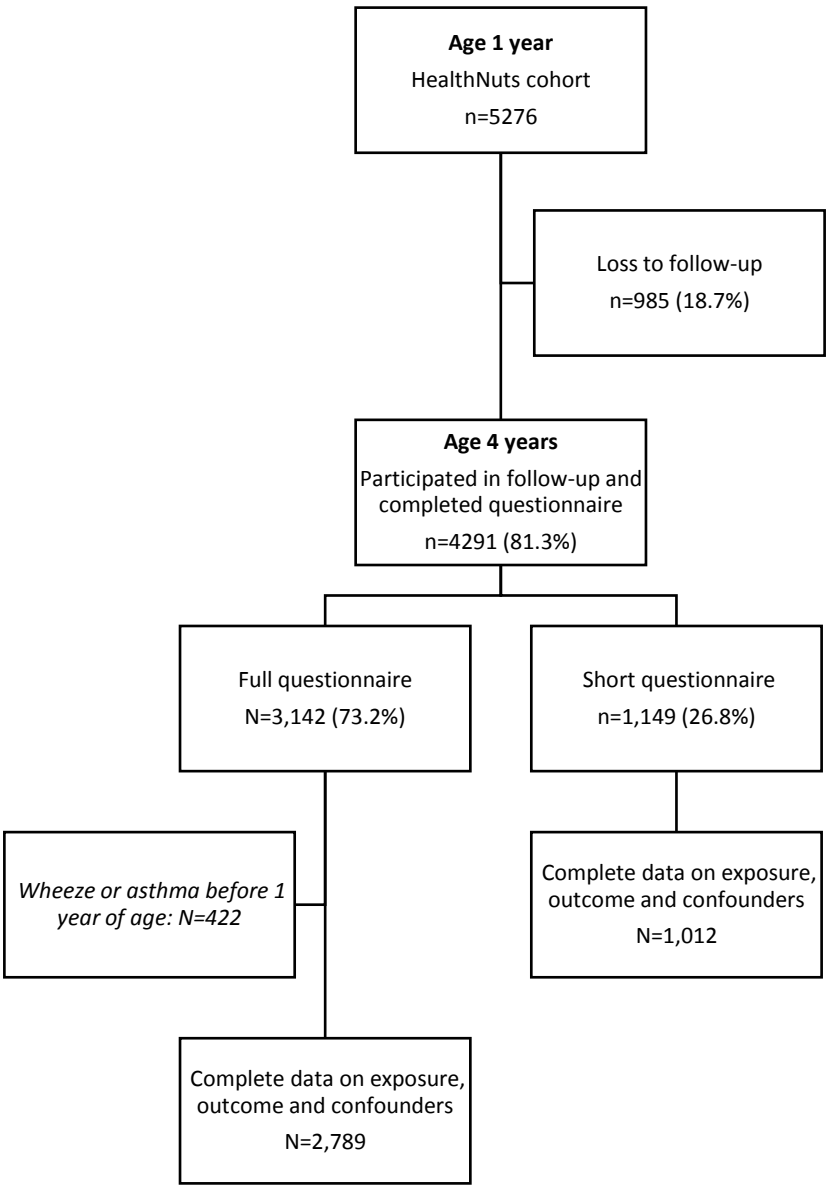
[‡]Persistent egg allergy: A positive oral food challenge (or recent reaction consistent with OFC stopping criteria) at both 1 and 4 years of age. A small number of participants who were eligible for but declined a food challenge at age 4 years were categorised as allergic for this analysis based on SPT wheal size ≥8mm and/or a reaction in the past 12 months consistent with IgE-mediated food allergy, as previously reported.(11)

Table IV. Relationship between eczema and food allergy at age 1 year and asthma at age 4 years

	Total	Asthma (%)	Relative risk (95%-CI)*	p-value
All infants				
No eczema or food allergy	1819	183 (10.1%)	1.0	-
Eczema only	497	85 (17.1%)	1.68 (1.32, 2.13)	<0.001
Food allergy only	127	21 (16.5%)	1.69 (1.12, 2.56)	0.012
Eczema and food allergy	223	63 (28.3%)	2.87 (2.22, 3.70)	<0.001
Excluding infants with wheeze or asthma in first year of life				
No eczema or food allergy	1394	115 (8.3%)	1.0	
Eczema only	344	35 (10.2%)	1.22 (0.86, 1.75)	0.26
Food allergy only	98	10 (10.2%)	1.29 (0.70, 2.38)	0.41
Eczema and food allergy	166	44 (26.5%)	3.27 (2.40, 4.47)	<0.001

*Adjusted for parents' country of birth, sex, socioeconomic status and family history of allergic disease.

Figure 1: Study participation and follow up at 4 years of age



Online Repository Text

Sensitivity analysis to explore the potential impact of missing data

We have previously described differences in the characteristics of the participants who completed the full questionnaire, the short questionnaire and non-participants at age 4 years. (16) Factors associated with completion of the full questionnaire rather than the short questionnaire or nonparticipation were the child's sex, socioeconomic status, family history of allergy, parents' country of birth and whether or not the child had a challenge-confirmed food allergy at age 1 year. To mitigate potential bias in estimated relative risk ratios due to differential participation in follow up, we generated sampling weights that were used to adjust for differences in these factors between participants with and without missing data at age 4 years, using the inverse probability weighting method described by Little and Rubin.(21) Weights were calculated as the inverse of the probability of inclusion at age 4 years, from a logistic regression model of participation including as covariates the child's sex, socioeconomic status, family history of allergy, parents' country of birth and whether or not the child had a challenge-confirmed food allergy at age 1 year. These weights were included in the logistic regression model (Online Repository Table E4), with robust standard errors used to ensure that the precisions of estimated relative risks reflected the sample size.

Online Repository Tables

Table E1: Sensitivity analysis - association between any food allergy at age 1 and various asthma outcome variables, among participants who completed either the full or the short version of the questionnaire.

Asthma definition and questionnaire type	Relative risk (95%-CI)*	p-value
Full questionnaire only (n=2,789)		
Parent report of asthma ever (n=409)	2.11 (1.72, 2.59)	<0.001
Parent report of asthma diagnosis ever (n=377)	2.08 (1.68, 2.57)	<0.001
Current asthma at age 4 yrs† (n=318)	2.15 (1.70, 2.73)	<0.001
Parent report of wheeze at age 4 years		
Any wheeze in past 12 mths (n=517)	1.83 (1.52, 2.19)	<0.001
4 or more episodes in past 12 mths (n=141)	3.41 (2.43, 4.79)	<0.001
Full and short questionnaire (n=3,801)		
Parent report of asthma or wheeze ever (n=970)	1.74 (1.53, 1.98)	<0.001

*Adjusted for parents' country of birth, sex, socioeconomic status and family history of allergic disease.

† Asthma diagnosis with either wheeze or asthma medication use in last 12 months.

Table E2: Sensitivity analysis - association between food allergy and eczema at age 1 and asthma diagnosis at age 4 years, using different definitions of eczema

	Relative risk (95%-CI)*	p-value
Parent report of eczema diagnosis		
No eczema or food allergy (n=1819)	1.0	-
Eczema only (n=497)	1.68 (1.32, 2.13)	<0.001
Food allergy only (n=127)	1.69 (1.12, 2.56)	0.012
Eczema and food allergy (n=223)	2.87 (2.22, 3.70)	<0.001
Broad eczema definition (eczema diagnosis, itchy rash treated with topical steroids, or nurse-observed eczema at 1 year of age)		
No eczema or food allergy (n=1485)	1.0	-
Eczema only (n=846)	1.59 (1.28, 2.00)	<0.001
Food allergy only (n=78)	1.09 (0.56, 2.12)	0.81
Eczema and food allergy (n=279)	3.04 (2.36, 3.91)	<0.001

*Adjusted for parents' country of birth, sex, socioeconomic status and family history of allergic disease.

Table E3: Relationship between food allergy at age 1 and asthma diagnosis at age 4, stratified by eczema and wheeze status in infancy

	Total	Asthma (%)	Relative risk (95%-CI)*	p-value
No eczema diagnosis in 1st year of life				
No food allergy	1819	183 (10.1%)	1.0	-
Food allergy	127	21 (16.5%)	1.68 (1.11, 2.52)	0.014
Eczema diagnosis in 1st year of life				
No food allergy	497	85 (17.1%)	1.0	-
Food allergy	223	63 (29.3%)	1.79 (1.34, 2.38)	<0.001
No wheeze in 1st year of life				
No food allergy	1836	168 (9.2%)	1.0	-
Food allergy	278	58 (20.9%)	2.32 (1.77, 3.04)	<0.001
Wheeze in 1st year of life				
No food allergy	366	91 (24.9%)	1.0	-
Food allergy	53	22 (41.5%)	1.68 (1.17, 2.41)	0.005

*Adjusted for parents' country of birth, sex, socioeconomic status and family history of allergic disease.

Table E4. Relationship between food sensitization and allergy at age 1 year and asthma at age 4 years, with sampling weights included in the model

	Relative risk (95%-CI)*	p-value
All infants		
Not sensitized	1.0	-
Sensitized tolerant	1.71 (1.02, 2.86)	0.042
Food allergic	2.19 (1.76, 2.72)	<0.001
Excluding infants with wheeze or asthma in first year of life		
Not sensitized	1.0	
Sensitized tolerant	2.04 (1.07, 3.88)	0.030
Food allergic	2.60 (1.97, 3.43)	<0.001

**Adjusted for parents' country of birth, sex, socioeconomic status and family history of allergic disease.*