Journal of Allergy and Clinical Immunology

The prevalence of food allergy and other allergic diseases in early childhood in a population-based study: HealthNuts age 4 follow-up.

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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. KJA. LG, AL, MW, JK and SD hold NHMRC awards.

Abstract: (300 words)

Background: The HealthNuts study previously reported interim prevalence data showing the highest prevalence of challenge-confirmed food allergy in infants internationally. However population-derived prevalence data on challenge-confirmed food allergy and other allergic diseases in preschool-aged children remains sparse. This study aims to report the updated prevalence of food allergy at age 1 year from the whole cohort, and to report the prevalence of food allergy, asthma, eczema and allergic rhinitis, at age 4 years.

Methods: HealthNuts is a population-based cohort study with baseline recruitment of 5276 1 year-old children who underwent SPT to 4 food allergens and those with detectable SPT had formal food challenges. At age 4 years, parents completed a questionnaire (81.3% completed) and those who previously attended the HealthNuts clinic at age 1 or reported symptoms of a new food allergy were invited for an assessment which included SPT and oral food challenges. Data on asthma, eczema and allergic rhinitis were captured by validated ISAAC study questionnaires.

Results: The prevalence of challenge-confirmed food allergy at age 1 and 4 years was 11.0% and 3.8%, respectively. At age 4 years peanut allergy prevalence was 1.9% for peanut (95% CI 1.6-2.3%), egg allergy 1.2% (95% CI 0.9-1.6%), and sesame allergy 0.4% (95% CI 0.2-0.6%). Late-onset peanut allergy at age 4 years was rare (0.2%). The prevalence of current diagnosed asthma was 10.8% (95% CI 9.7-12.1%), current eczema 16.0 % (95% CI 14.7-

17.4%) and current allergic rhinitis 8.3% (95% CI 7.2-9.4%). 40-50% of this population-based cohort experienced symptoms of an allergic disease in the first 4 years of their life. *Conclusion:* Although the prevalence of food allergy decreased between ages 1 and age 4 years in this population based cohort, the prevalence of any allergic disease amongst 4 year old children in Melbourne, Australia, is remarkably high.

Key messages:

Although the prevalence of challenge-confirmed food allergy has reduced from 11% to 3.8% between ages 1 and 4 years in this population-based cohort, the prevalence of any allergic disease amongst 4 year old children in Melbourne, Australia, is remarkably high.

Capsule summary:

This study reports the prevalence of challenge-confirmed food allergy and other allergic disease in a population-based longitudinal study of children at ages 1 and 4 years.

Keywords:

Allergy, asthma, eczema, egg allergy, food allergy, allergic rhinitis, HealthNuts, longitudinal study, peanut allergy, prevalence, population-based study, sesame allergy.

Abbreviations:

ISAAC: International Study of Asthma and Allergies in Childhood

OFC: oral food challenge

SPT: skin prick test

sIgE: specific-IgE

Word count: 4173

Introduction:

An increase in the prevalence of allergic diseases has been reported internationally, initially marked by an increase in asthma, eczema and allergic rhinitis, peaking in the 1990s to 2000s. This was followed by the "second wave" of the allergy epidemic with an increase in reported food allergies over the last 2 decades. (1-4) As such, allergic diseases are now recognised as a significant public health concern in many developed countries.

Until recently, the prevalence of food allergy has been difficult to estimate due to the absence of large-scale, population-based studies using challenge-confirmed food allergy outcomes. Accurate measurement of the prevalence of food allergy using gold-standard outcomes is essential for tracking changes in prevalence over time. Previously, food allergy studies have relied on self-report or measures of sensitisation, both of which are known to overestimate the prevalence of food allergy. One of the first studies to use a population-based sampling frame and systematic approach to measuring food allergy using the gold standard oral food challenge (OFC), irrespective of skin prick test (SPT) wheal size, was the HealthNuts study in Melbourne, Australia. (5) We reported on the prevalence of food allergy when 2800 participants had been recruited into the study and found that more than 10% had challenge-confirmed food allergy at age 1 year, which is higher than emerging prevalence reports in other countries which range from 1% to 6%. (5-11) However, these estimates are largely derived from infants and the population-based prevalence of challenge-confirmed food allergy in older children remains largely unknown.

The aims of this study are to report the updated prevalence of food allergy at age 1 year from the whole cohort, and to report the prevalence of challenge-confirmed food allergy and other allergic diseases including asthma, eczema and allergic rhinitis, at age 4 years.

Methods:

Study design:

Recruitment:

The HealthNuts study is a population-based, longitudinal food allergy study undertaken in Melbourne, Australia. The recruitment methods have been described in detail previously. (12, 13) Briefly, 5276 12-month-old infants were recruited (74% participation) from council-run immunization sessions where they underwent SPT screening to four common food allergens, egg, peanut, sesame and either cow's milk or shrimp. Any infant with a detectable SPT (≥ 1mm) was invited for a food challenge at Melbourne's Royal Children's Hospital. SPT was repeated on the day of challenge and blood was taken to measure serum-specific IgE (both of which were used to define sensitization status). If SPT was negative (0mm) at community recruitment, infants were considered to be food tolerant. To test this assumption, a random sample of 200 SPT 0mm infants underwent OFC to egg or peanut and all were tolerant.

Age 4 follow-up:

The first longitudinal follow-up on the entire cohort was undertaken in the child's 4th year, as previously described. (12) Parents were mailed a questionnaire which captured information on the child's diet, adverse reactions to foods, other allergy symptoms, environmental exposures and quality of life. Questions on key allergic outcomes (asthma, eczema and allergic rhinitis) included those from the validated ISAAC study. If parents did not return the questionnaire a reminder system was followed 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.

Two pathways triggered an invitation for clinical assessment. Any child who had previously attended the HealthNuts study clinic at age 1 was invited for a clinical allergy assessment. In addition, if parents reported in a questionnaire that their child had reacted to a food since age 12 months, and telephone screening by a study nurse revealed that the symptoms were consistent with IgE-mediated food allergy, the child was also invited to the study clinic for an allergy assessment. If parents reported symptoms that were not consistent with IgE-mediated food allergy, or that the symptoms were no longer occurring and the child could tolerate the food, children did not undergo further assessment.

The clinical allergy assessment consisted of clinical history, SPT, blood test for sIgE and possible OFC. If the child had a positive OFC at age 1, they underwent repeat OFC at age 4 to test for the persistence or resolution of food allergy. Children who were sensitized to a food but had a negative OFC at age 1, and those who reported symptoms of a new food allergy initially underwent SPT. If SPT demonstrated evidence of sensitisation and there was not a history of ingestion and tolerance, or if there was a history of ingestion and reaction, participants were offered OFC to these foods. Children did not participate in an OFC if they had a reaction to the index food within the previous 1 month for egg or 2 months for peanut and sesame that was consistent with our OFC-stopping criteria and were considered food allergic. OFC, SPT and sIgE at age 1 and 4 years followed the same protocol. (12)

Skin prick tests and serum specific-IgE:

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). Blood samples were collected at both ages and plasma was isolated for sIgE assays using the ImmunoCAP System FEIA (Phadia AB, Uppsala, Sweden).

Oral food challenges:

OFCs were conducted as previously described with challenge staff blinded to SPT wheal size and previous clinical history. (13, 14) 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 single serving of the challenge food at home for 7 days to capture any late reactions. Additional information on the clinical assessments (SPT and OFC) are included in this articles online repository.

Definitions for age 1 allergy outcomes

Challenge-confirmed food allergy: Positive OFC (or recent reaction consistent with OFC stopping criteria) and positive test of sensitization (SPT $\geq$ 2mm and/or sIgE $\geq$ 0.35 kU/L)

Food tolerance: Negative OFC or SPT 0mm at community recruitment

Eczema diagnosis: Parent-report of a doctor diagnosis of eczema

Wheeze: Parent report of wheeze ever in the first year of life

Definitions for age 4 allergy outcomes

Challenge-confirmed food allergy: Positive OFC (or recent reaction consistent with OFC stopping criteria) and positive test of sensitization (SPT $\geq$ 3mm and/or sIgE $\geq$ 0.35 kU/L);

Food tolerance: Negative OFC; or food tolerant (or missing) at age 1 and did not present through age 4 screening process with a new food allergy.

Probable and possible food allergy and tolerance: A small number of participants who were eligible for but declined a food challenge were assigned a probable or possible food allergy status based on the SPT responses and/or clinical history (see online repository methods section and figure E1for full definitions).

The definitions for other allergic outcomes obtained from the full questionnaire, using the ISAAC questions, are as follows (see this articles online repository Table E2 for a full list of questions and definitions).

Asthma ever: parent-report of asthma ever

Asthma diagnosis: parent-report of doctor-diagnosis of asthma ever

Current asthma: asthma diagnosis and either wheeze or asthma medication use in last 12 months

Wheeze ever: parent-report of wheeze ever

Current wheeze: parent-report of wheeze in the last 12 months

Itchy rash ever: parent-report of an itchy rash ever

Eczema diagnosis ever: parent-report of a doctor diagnosis of eczema ever

Current eczema: parent-report of an itchy rash in the last 12 months that affected typical eczema locations e.g. folds of elbows and knees

Nose symptoms ever: sneezing or runny/blocked nose when child did not have cold/flu

Nose symptoms current: nose symptoms in the last 12 months

Current allergic rhinitis: nose symptoms in the last 12 months that was accompanied by itchy watery eyes

Allergic rhinitis ever: Parent-report that their child had had allergic rhinitis ever

Allergic rhinitis diagnosis ever: parent-report of a doctor diagnosis of allergic rhinitis ever

Ethical Conduct in Human Research:

Approval to conduct the HealthNuts study was obtained 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:

The population prevalence of each binary outcome variable was estimated as the observed proportion, with confidence intervals calculated assuming a binomial sampling distribution. Data on all age 1 outcomes and food allergy at ages 1 and 4 are presented for the whole cohort, whereas analyses on other allergy age 4 outcomes were primarily conducted on participants who completed the full written questionnaire. To assess for potential selection bias in presentation of the age 4 outcomes on the reduced cohort, characteristics of the participants who completed the full questionnaire, short questionnaire and non-participants were compared using Pearson's chi-square test. To assess whether the prevalence estimates were influenced by characteristics that were associated with participation at age 4, we calculated sampling weights that were used to adjust via re-weighting the observed prevalence to reflect the distribution of risk factors among those approached to consider participation rather than among only those who completed the full questionnaire. The weights were the inverse of the predicted probability of participation obtained after fitting a logistic regression model including as covariates risk factors that were associated with completion of the full questionnaire rather than the short questionnaire or non-participation (child's sex,

socioeconomic status, family history of allergy, parents country of birth and whether or not the child had challenge-confirmed food allergy at age 1), that is, we calculated a propensity score for each participant. (15) A sensitivity analysis was also conducted where the prevalence of allergies were calculated separately amongst respondents of the full and short questionnaire. Prevalence estimates were combined where an identical question was asked in both the full and short questionnaire.

Results:

Participation:

Participation in the HealthNuts study at age 1 year has been described in detail previously, therefore Figure 1 describes participation in the age 4 follow-up. (5, 12, 13, 16) At age 4 years, 81.3% of parents completed a questionnaire (n=4291); of these 73% completed the full questionnaire and 27% completed a short telephone questionnaire. Among children who were food allergic at age 1 (n=539), 89% completed a questionnaire and of those, 65% attended the HealthNuts study clinic for assessment. Parent's reported symptoms of a new reaction to a food since age 1 year in 472 children, however following telephone screening to rule out likely non-IgE-mediated or resolved reactions, only 159 attended the study clinic for assessment and 81 underwent OFC. Overall, 592 children attended the study and 356 underwent OFC to one or more foods. OFC were most commonly undertaken to the following 4 foods, egg (n=190), peanut (n=147), cashew (n=80) and sesame (n=36). (See Table E1 in this article's online repository for a list of OFC undertaken to other foods.)

Demographics of the cohort, including differences in characteristics between responders and non-responders at age 4 are described in Table 1. Children with food allergy at age 1, a family history of allergy, Australian-born parents and a higher socioeconomic status, were more likely to participate at age 4. There were few characteristic differences between food-allergic children who did and did not attend the study clinic at age 4; attendees were more likely to have Australian-born parents, eczema at age 1 and other allergies at age 4. (Table E2 online repository)

Food allergy:

Table 2A presents the updated prevalence of challenge-proven food allergy using the entire cohort (n=5276). At age 1 year the prevalence of peanut allergy was 3.1% (95% CI 2.7-3.6%), egg allergy was 9.5 (95% CI 8.7-10.3%), sesame allergy 0.6 (95% CI 0.5-0.9%) and cow's milk was 1.5 (95% CI 1.1-2.1%).

At age 4 years, using our strictest definition of challenge-confirmed food allergy, the prevalence of peanut allergy was 1.9% (95% CI 1.6-2.3%), egg 1.2% (95% CI 0.9-1.6) and sesame allergy 0.4% (95% CI 0.3-0.6%) (Table 2B). Using the less stringent definitions, the prevalence of probable and possible food allergies was similar to each other. As expected, the prevalence of challenge-confirmed food allergy to any food at age 4 years was lower than that at age 1 year, 3.8% (95% CI 3.3-4.4%) versus 11.0% (95% CI 10.1-11.9%) respectively (Figure 2).

Late-onset food allergies:

There were 12 (0.2%) cases of late-onset challenge-confirmed peanut allergy at age 4 years among children who were assessed as tolerant to peanut at age 1 year; seven of these children were SPT negative to peanut at age 1. A further 6 cases of peanut allergy were confirmed at age 4 in children who had an inconclusive peanut allergy status at age 1. There were 4 cases of late-onset sesame allergy and no cases of late-onset egg allergy. Cashew was the most commonly presenting new food allergy at age 4 (n=48); 34 cases of cashew allergy occurred in children who were allergic to other foods at age 1 and a further 9 and 5 cases occurred in children who's food allergy status was tolerant or missing at age 1, respectively. SPT was available in 44 of these children at age 1 and 34 were sensitized to cashew at age 1.

Asthma and wheeze:

Estimates reported for the allergic outcomes of asthma, eczema and allergic rhinitis are the weighted-population prevalence to better reflect the full sample. Among respondents of the full questionnaire (n=3142), the prevalence of a parent-reported doctor-diagnosis of asthma ever was 13.8% (95% CI 11.6-14.1%) and the prevalence of current asthma was 10.8% (95% CI 9.7-12.1) (Table 3). A higher proportion reported that their child had experienced a wheezing episode ever, 27.0% (95% CI 25.4-28.7) and nearly one in five children had experienced a wheezing episode in the preceding 12-months (18.0%, 95% CI 16.6-19.5%). Few parents reported severe wheeze symptoms.

Eczema:

At 4 years of age, 27.6 % (95% CI 26.0-29.3) of parents reported that their child had ever been diagnosed with eczema by a doctor. This was similar to the prevalence of doctor-diagnosed eczema at age 1 year, 26.6% (25.4-27.8) although among those with a diagnosis of eczema at age 4, 33% had new-onset eczema and had not reported a diagnosis of eczema at 12-months of age. The prevalence of current eczema with active symptoms in the last 12 months was 16.0% (95% CI 14.7-17.4%).

Allergic rhinitis:

The prevalence of parent-reported allergic rhinitis ever was 11.4% (95% CI 10.2-12.7) while the prevalence of doctor-diagnosed allergic rhinitis was lower (3.6%, 95% CI 2.9-4.4). A higher proportion reported that their child had sneezing, runny or blocked nose when they did not have a cold or flu (19.3%, 95% CI 17.8-20.8%) and most reported that these symptoms had occurred in the previous 12 months (16.9%, 95% CI 15.5-18.4%). The prevalence of

current allergic rhinitis (current nose symptoms and itchy eyes) was 8.3% (95% CI 7.2-9.4%),

Prevalence of allergic disease in the first 4 years of life:

The prevalence of any allergic disease (challenge-confirmed food allergy or doctor-diagnosed eczema) at age 1 year was 32.1% (95% CI 30.8-33.5%). This was similar to prevalence of current allergic disease (challenge-confirmed food allergy or current asthma, eczema or allergic rhinitis) at age 4 years, 28.2% (95% CI 26.5-29.9%, n=927/3135).

Using only participants with complete data on the following variables, challenge-confirmed food allergy, doctor diagnosed allergies ever (asthma, eczema or allergic rhinitis), or current allergies (asthma, eczema or allergic rhinitis) (n=2907), 50.5% (95% CI 48.7-52.3%) of children reported at least one allergic disease in the first 4 years of life (Figure 3). Most children, 31.1%, reported only one allergy, the corresponding figures for 2, 3 and 4 allergies were 13.8%, 4.6% and 0.9% respectively. Of those that reported an allergic disease, 62% had 1 condition, 27% had 2, 9% had 3 and 2% had 4 allergic diseases. When including participants from the whole cohort with a report of at least one allergy (challenge-confirmed food allergy, doctor-diagnosed or current allergies) and including those with missing data on one or more allergies in the denominator, 40.9% (95% CI 39.6-42.2) of children reported at least one allergic disease in the first 4 years of life (n=2152/5264). Again, most children were only diagnosed with only one allergy, 28.0%, the corresponding figures for 2, 3 and 4 allergies were 9.7%, 2.7% and 0.5% respectively. . The overlap of allergic disease at age 1 and 4 is presented in Figure 4.

Sensitivity analysis:

Results of the short telephone questionnaire, (n=1149) and combined estimates of both questionnaire are presented in Table E3 in this articles online repository. The prevalence of allergies was higher among those who completed the full questionnaire compared to the short questionnaire, with the exception of a doctor-diagnosis of allergic rhinitis. When combining the estimates, the prevalence of allergic diseases only changed slightly from those reported from full questionnaire responses only.

Discussion

In this longitudinal population-based cohort, the prevalence of food allergy fell by two thirds from 11% at age 1 to 3.8% at age 4 years with resolution of egg allergy the main driver of this change, dropping from 9.5% to 1.2%. The prevalence of peanut allergy also fell between 1 and 4 years, dropping from 3.1% to 1.9%. Despite this drop, peanut allergy was the most prevalent food allergy in 4-year-old children. The prevalence of parent-reported doctor-diagnosed eczema was stable with 27.6% reporting a diagnosis of eczema ever in the first 4 years of life, while 16.0% reported current eczema, experiencing eczema symptoms in the past 12 months. The prevalence of current asthma and allergic rhinitis was 10.8% and 8.3% respectively. Significantly, overall nearly half the cohort experienced symptoms of an allergic disease in the first 4 years of their life (40% to 50%).

The strengths of this study are the large sample size, population-based sampling frame and high-participation rate at both recruitment and follow-up (74% and 81% respectively). Population sampling ensures that we have captured the full spectrum of food allergy at the community level rather than relying on samples from tertiary referral centres, which may be over-represented by children with more severe allergic disease. Unlike many previous food allergy studies, this study used the gold-standard OFC to objectively measure food allergy, irrespective of SPT wheal size, ensuring robust classification of true food allergy. In addition, OFCs were conducted at specific ages as opposed to previous retrospective studies on the natural history of food allergy, which often contain children of mixed age groups and irregular follow-up periods.

Several limitations of this study are acknowledged. Although the participation rate was high, there were some differences in characteristics between participants and non-participants at age 4 years which resulted in the present cohort being over-represented by participants with a family or personal history of allergic disease. To overcome this attrition bias, we have reported key estimates for asthma, eczema and allergic rhinitis at age 4, which were obtained from participants of the full questionnaire only, as both observed proportions and population-prevalences weighted for factors that were associated with participation (sex, socioeconomic status, family and personal history of allergy and parent's country of birth). The prevalence of allergic outcomes at age 1 and food allergy at age 4 were reported for the entire HealthNuts cohort. At recruitment, a non-responder questionnaire was conducted to assess potential selection bias for participation in the HealthNuts study. The most common reason for parents declining to participate in the study was because the SPT involved too many needles (28%), followed by that the child was already eating and tolerating the foods tested (25%). Only 2.9% of responders reported that the child had already been diagnosed with food allergy. Therefore, it is more likely that parents chose not to participate in the study because of known tolerance rather than known allergy. In previous publications we have weighted our key findings at age 1 year to be reflective of the general population using the non-responder questionnaire, including previous food reactions ,and found that our estimates only altered marginally (prevalence of peanut and egg allergy changed from 2.9% to 3.0% and 9.0 to 8.9% upon back-weighting (5)) In addition, we have previously shown that the HealthNuts cohort has good external validity and is representative of the general population in Melbourne, Australia. (13) These two factors suggest that selection bias in this study is minimal, hence we did not back-weight the prevalence of age 1 outcomes or food allergy at age 4. Due to absence of data on parents country of birth for non-responders, the age 4 estimates were not further back-weighted to reflect non-responders.

As some participants declined to undergo a food challenge at age 4, a definitive diagnosis of persistent or resolved food allergy could not be ascertained for all individuals food allergic at age 1 year. To overcome this, we used SPT, clinical and/or questionnaire data to assign a probable or possible food allergy or tolerance status to these participants and a food allergy status was assigned to 84-89% of participants at age 4 who were food allergic at age 1 year (depending on the food, see figure E1 in this article's online repository). The prevalence of food allergy has been presented using all 3 definitions; estimates are similar and the confidence intervals overlap. We have chosen to highlight the definite food allergy outcome throughout the manuscript as it is the most robust estimate of food allergy relying on challenge-proven food allergy outcomes and it does not differ significantly from the less robust definitions. In addition, children who were food tolerant at age 1 year that did not participate in age 4 follow-up were assumed to remain tolerant at age 4 years as the prevalence of late-onset food allergy was very low. To test this assumption, a sensitivity analysis was conducted and the prevalence of food allergy at age 4 years was calculated excluding these participants. When these prevalence's were back-weighted to the whole cohort, prevalence estimates were nearly identical (table E4 in online repository). Our estimates of the prevalence of allergic disease in the first 4 years of life may both under- or over-estimate the true value. Using participants with only complete data on all allergic outcomes included only participants who completed age 4 follow-up and may be biased towards more allergic disease. Likewise by including participants with missing data on age 4 outcomes as non-allergic, we may underestimate the true value as children may be incorrectly classified as never allergic because we have not captured those who went on to develop allergies but were lost to follow-up. Therefore, we believe that the true value lies somewhere between our two estimates.

Although the gold-standard was used to measure food allergy, we relied on questionnaire data to describe the other allergic conditions. Estimating the prevalence of other allergies in childhood is difficult due to both the absence of gold standard tools that are accessible in large-scale population-based studies and due to the heterogeneity of disease expression itself. Validated questionnaires are therefore commonly used. Our questionnaires included validated questions from the ISAAC study to capture information of allergic diseases, as well as parental report of a doctor diagnosis. The ISAAC questionnaire was validated among 6-7 year old children and unfortunately the validity of these questions in a younger age group is not known, therefore our estimates should be interpreted within this context. Objectively measuring asthma at the population level is challenging due to the absence of a gold standard test and heterogeneity in the presentation of asthma, which is now regarded as a broad syndrome with multiple phenotypes. (17, 18) We utilised parent-report of doctor-diagnosis of asthma in conjunction with current symptoms and/or medication used to describe the prevalence of asthma, however we acknowledge that reporting asthma in this age group may be problematic as it can be difficult to untangle true asthma from early transient wheeze of viral origin. Previous reports have found that self-reported doctor diagnosis of asthma has high specificity and medium-high sensitivity when compared to clinical methods although there is also evidence to suggest that milder symptoms may be classified as asthma. (17, 19)

We previously published the prevalence of food allergy from this cohort when only the first half the cohort had been recruited. Our prevalence estimates for the whole cohort are slightly higher than our initial prevalence publication, although still within the confidence intervals, (5) despite documented evidence for earlier introduction of solids (including peanut and egg) in the cohort across this time period. (20) At the time of this study's inception there were no

food allergy prevalence studies using population-based sampling and challenge proven outcomes. Our reports of food allergy prevalence, particularly egg, were unexpectedly high which may be reflective of the young age of our age baseline sample. It should also be noted that we used the most allergenic form of egg (raw egg) to estimate prevalence at age 1 year. However we also used this form of challenge at age 4 years and still found a significant drop in prevalence. The prevalence of peanut allergy fell from 3.1% to 1.9% between ages 1 and 4 years and egg allergy fell from 9.5% to 1.2%. This is consistent with previous research that approximately 20% of children will outgrow peanut allergy and 80% will develop tolerance to egg.(21, 22) As this cohort has aged and overall nearly two thirds of food allergy has resolved, our prevalence estimates are now closer, although still higher, than international reports. In recent years, new studies have emerged using population-based sampling frames and challenge-proven outcomes. In a birth cohort of 12,000 infants from 9 countries in Europe, the Europrevall consortium reported a prevalence of challenge-proven food allergy in the first 2 years of life of 0.59% (95% CI 0.43-0.80) and 1.23% (95% CI 0.98-1.51) for milk and egg respectively. In South Africa, the prevalence of food allergy to any food in children aged 12 to 36 months was 2.5% (95% CI 1.2-3.9), egg 1.8% and peanut 1.2% (8) In China the prevalence of any food allergy among infants aged up to 12 months was 3.8% (95% CI 2.5-5.9), with a prevalence of 2.5% to egg and 1.3% to cow's milk. (9) Recently in Ireland, the BASELINE birth cohort reported the prevalence of challenge-confirmed food allergy in infants up to age 2 years was 4.5% for any food, 2.9% for egg and 1.8% for peanut. (10)

The prevalence of other allergic diseases in this cohort is higher than that reported internationally, although it is well recognised that developed countries carry a greater burden of allergic disease. In 2001-3, the International Study of Asthma and Allergies in Childhood (ISAAC) reported a global prevalence for current asthma, allergic rhinitis and eczema of

11.7%, 8.5% and 7.9%, respectively, in 6-7 year old children. (23) For Australia specifically, the ISAAC study reported the prevalence of current wheeze in 6-7 year old children to be > 20%, which is similar to our finding of 18.0%. (24) The prevalence of current eczema in 6-7 year old children was higher in Australia than the global estimate, 17.1% had current eczema (years 2001-2003) which is similar to the results reported in the present study suggesting that the prevalence of eczema has stabilised in the last decade (25). The prevalence of current allergic rhinitis in 6-7 year old children in ISAAC was 13.5% which is higher than our reported prevalence of 8.3%; this difference may be reflective of the difference ages of the cohorts. (26)

A longitudinal study of 4000 children in Sweden, which used similar definitions for allergic disease (parent-report of doctor diagnosis) with the exception of food allergy (challenge-confirmed in the present study) (27) reported a decreasing prevalence of any allergy at age 1 and 4 years from 26% to 15% respectively. However, in the present study, we found the prevalence of any allergy at age 1 year and current allergy at age 4 to be similar, 32.1% and 28.2% respectively.

In conclusion, although the prevalence of challenge-confirmed food allergy has reduced between ages 1 and 4 years, Melbourne, Australia continues to report high rates of food allergy, eczema and asthma compared to international estimates with approximately 40-50% of the cohort reporting an allergic disease in the first 4 years of life.

Table 1: Demographics of the HealthNuts cohort including an assessment of differences in characteristics between those who completed the full versus short questionnaire and non-participants in age 4 follow-up

	Full questionnaire (n=3142)	Short questionnaire (n=1149)	Did not participate (n=985)	P
Sex (male)	51.2	49.4	51.4	0.54
Mode of delivery (caesarean)	34.1	31.4	32.6	0.23
Preterm birth	5.9	6.9	5.9	0.45
Socioeconomic status				
1 (most disadvantaged)	15.8	25.9	27.5	<0.001
2	20.0	20.7	18.9	
3	22.0	20.7	18.0	
4	21.4	16.2	16.7	
5	20.9	16.5	18.9	
Parent country of birth				
Both Australian	64.8	52.8	49.0	<0.001
One or both Asian	11.6	21.9	23.0	
Other	23.6	25.2	28.0	
Family history				
Any allergy	62.4	72.1	67.8	<0.001
Food allergy	12.4	8.8	9.9	0.003
Eczema	32.1	29.6	26.8	0.006
Asthma	31.3	32.3	26.8	0.01
Age in years (mean (s.d.))				
Recruitment	1.05 (0.06)	1.06 (0.06)	1.06 (0.07)	0.001
Follow-up	4.14 (0.19)	4.32 (0.19)	-	<0.001
Any food allergy at age 1 year	13.0	8.1	6.9	<0.001
Egg allergy	11.1	7.2	6.5	<0.001
Egg sensitised (SPT ≥ 2mm)	14.0	13.7	12.2	0.33
Peanut allergy	4.0	1.6	1.9	<0.001
Peanut sensitised (SPT ≥ 2mm)	8.1	6.8	7.1	0.29
Sesame allergy	0.9	0.4	0.3	0.09
Sesame sensitised (SPT ≥ 2mm)	1.9	1.9	1.8	0.98
Eczema in first year of life	27.6	25.0	25.3	0.15
Wheeze in first year of life	16.2	21.6	18.8	<0.001*
Any siblings	49.9	53.3	48.8	0.08

* When comparing only participants (full and short questionnaire combined) and non-participants, there was no significant difference between wheezing in the first year of life (17.6% versus 18.8 %, p=0.43) and it was not including in calculation of sampling weights

492 Table 2A: The prevalence of allergic outcomes at age 1 year.

Allergic outcome	n/N[1]	Prevalence % (95% CI)
Peanut sensitization	390/5129	7.6 (6.9-8.4)
Peanut allergy	158/5083	3.1 (2.7-3.6)
Egg sensitization	696/5127	13.6 (12.7-14.5)
Egg allergy	472/4983	9.5 (8.7-10.3)
Sesame sensitization	96/5091	1.9 (1.6-2.3)
Sesame allergy	33/5097	0.6 (0.5-0.9)
Any challenge-confirmed food allergy[2]	539/4912	11.0 (10.1-11.9)
Cow's milk sensitization	60/2715	2.2 (1.7-2.8)
Cow's milk allergy[3]	40/2592	1.5 (1.1-2.1)
Shrimp sensitization	14/2405	0.6 (0.3-1.0)
Eczema diagnosis	1325/4982	26.6 (25.4-27.8)
Wheeze	821/4603	17.8 (16.7-19.0)

493 1. The denominator varies for each outcome because data was excluded for the following reasons: missing
494 data, inconclusive OFC results, absence of OFC in sensitized individuals, or "not sure" questionnaire
495 responses for wheeze and eczema. SPT to shrimp and cow's milk was only undertaken on half the cohort.
496 2. Any food allergy includes egg peanut and sesame only, does not include cow's milk allergy because it was
497 not food challenge confirmed
498 3. OFC were not conducted to cow's milk. Cow's milk allergy was defined as cow's milk sensitized on SPT
499 or sIgE plus a parent-report of a reaction consistent with IgE-mediated food allergy
500

501 Table 2B: The prevalence of food allergy at age 4 years using three definitions of food
502 allergy.
503

	Definite allergy % (95% CI)	Probable allergy % (95% CI)	Possible allergy % (95% CI)
PEANUT	n=5062[1]	n=5093[1]	n=5109[1]
Never peanut allergic	96.9	96.3	96.0
Resolved peanut allergy	0.4	0.6	0.6
Persistent peanut allergy	1.6	1.8	2.1
Late-onset peanut allergy	0.2	0.3	0.3
Allergic age 4, age 1 missing[2]	0.1	0.2	0.2
Tolerant age 4, age 1 missing[2]	0.8	0.8	0.8
Prevalence	1.9 (1.6-2.3)	2.3 (1.9-2.8)	2.7 (2.3-3.2)
EGG	n=4819[1]	n=4978[1]	n=4992[1]
Never egg allergic	93.6	90.6	90.3
Resolved egg allergy 2y[3]	1.8	1.8	1.7
Resolved egg allergy 4y	1.8	4.4	4.4
Persistent egg allergy 4y	1.1	1.6	1.9
Allergic age 4, age 1 missing[2]	0.1	0.2	0.2
Tolerant age 4, age 1 missing[2]	1.6	1.5	1.5
Prevalence	1.2 (0.9-1.6)	1.8 (1.4-2.2)	2.0 (1.7-2.5)
SESAME	n=5138[1]	n=5143[1]	n=5144[1]
Never sesame allergic	98.4	98.3	98.3

Resolved sesame allergy	0.1	0.2	0.2
Persistent sesame allergy	0.3	0.3	0.4
Late-onset sesame allergy	0.08	0.08	0.06
Allergic age 4, age 1 missing[2]	0.04	0.06	0.04
Tolerant age 4, age 1 missing[2]	1.1	1.1	1.1
Prevalence	0.4 (0.3-0.6)	0.5 (0.3-0.7)	0.5 (0.3-0.7)
ANY FOOD ALLERGY[3]			
Prevalence	3.8 (3.3-4.4) (n=182/4757)	4.4 (3.9-5.1) n=217/4838)	5.1 (4.5-5.7) n=250/4923

1. Missing food allergy status at age 1 may be due to missing data, sensitization at community recruitment but did not attend OFC, inconclusive OFC or positive OFC but non-sensitized (egg=21, sesame=3).
2. Denominators for the age 4 food allergy definitions differ because some participants who had a missing or inconclusive definite food allergy status were assigned a probable or possible food allergy (see definitions).
3. A subset of infants with positive OFC to raw egg at age 1 participated in a sub-study which included a repeat OFC to raw egg at age 2 years. As approximately 50% of these children had developed tolerance to raw egg by age 2 years, they did not participate in repeat OFC at age 4 years although information about their ongoing dietary tolerance to egg was assessed. These participants and methods have been described in detail previously. (11)
4. Participants were included if in the numerator if they were allergic to one or more foods, including additional foods tested (see online repository table E2); participants were excluded from the denominator if they were tolerant to one food but missing a food allergy status to another because we could not definitively conclude that they were food tolerant.

519 Table 3: Prevalence of allergic disease reported in 4 year old children among those that
520 completed the full questionnaire (n=3142)

	n/N	Observed proportion % (95% CI)	Population prevalence[1] % (95% CI)
ASTHMA			
Parent-report asthma	458/3050	15.0 (13.8-16.3)	13.9 (12.7-15.3)
Doctor-diagnosis of asthma	423/3047	13.8 (12.7-15.1)	13.8 (11.6-14.1)
Current asthma	359/3047	11.8 (10.7-13.0)	10.8 (9.7-12.1)
Wheeze ever	844/3021	27.9 (26.3-29.6)	27.0 (25.4-28.7)
Current wheeze	573/3022	18.9 (17.6-20.4)	18.0 (16.6-19.5)
Current wheeze frequency			
1-3 episodes / year	393/3016	13.0 (11.9-14.3)	12.6 (11.4-13.9)
4-12 episodes / year	127/3016	4.2 (3.5-5.0)	3.6 (3.0-4.4)
>12 episodes / year	32/3016	1.1 (0.8-1.5)	1.1 (0.8-1.6)
Current wheeze disturbs sleep			
Less than once per week	270/3003	9.0 (8.0-10.1)	8.5 (7.6-9.7)
More than once per week	63/3003	2.1 (1.6-2.7)	2.1 (1.6-2.7)
Current wheeze limits speech	109/3008	3.6 (3.0-4.3)	3.3 (2.7-4.0)
Current medication use for wheeze or asthma[2]	438/2814	15.6 (14.3-16.9)	15.0 (13.6-16.4)
ECZEMA			
Doctor-diagnosis of eczema ever	886/3058	29.0 (27.4-30.6)	27.6 (26.0-29.3)
Itchy rash ever	745/3019	24.7 (23.2-26.2)	23.4 (21.8-25.0)
Current eczema	508/3019	16.8 (15.5-18.2)	16.0 (14.7-17.4)
Current eczema disturbs sleep			
Less than once per week	143/3015	4.7 (4.0-5.6)	4.6 (3.9-5.5)
More than once per week	50/3015	1.7 (1.2-202)	1.6 (1.2-2.2)
ALLERGIC RHINITIS			
Doctor-diagnosis of allergic rhinitis	110/3016	3.6 (3.0-4.4)	3.6 (2.9-4.4)
Parent-report allergic rhinitis	350/3016	11.6 (10.5-12.8)	11.4 (10.2-12.7)
Nose symptoms ever	576/2928	19.7 (18.3-21.2)	19.3 (17.8-20.8)
Nose symptoms current	504/2915	17.3 (16.0-18.7)	16.9 (15.5-18.4)
Current allergic rhinitis	238/2842	8.4 (7.4-9.5)	8.3 (7.2-9.4)

521 1. Prevalence estimates for the broader Melbourne population, which were calculated by weighting the
522 proportion of the participants who completed the full questionnaire at age 4 using sampling weights
523 equal to the inverse probability of the family participating in the study at age 1 year.
524 2. Medication use for wheeze or asthma includes reliever, preventers and oral steroids
525

Figure 1. Participation in HealthNuts Wave 2, the age 4 follow-up

Figure 2: The prevalence of challenge-confirmed food allergy at age 1 and 4 years in a population-based cohort (n=5276)

Figure 3: Number of allergic diseases experienced by children in the first 4 years of life for the whole cohort (n=5276 which includes participants who are missing an outcome for one or more allergies for example by not participating in age 4 follow-up) and those with complete data on all 4 allergies (n=2907)

Figure 4A: Venn diagram depicting the overlap of current allergic diseases in 1 year-old infants (the size of the circle are proportional to the outcome)

Figure 4B: Venn diagram depicting the overlap of current allergic disease in 4-year-old children (among those with complete data for all 3 variables; excluding allergic rhinitis)

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