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

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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 remain sparse.

Objective: This study aimed 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 one-year-old children who underwent skin prick test (SPT) to 4 food allergens and those with detectable SPT results 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 year or reported symptoms of a new food allergy were invited for an assessment that included SPT and oral food challenges. Data on asthma, eczema, and allergic rhinitis were captured by validated International Study of Asthma and Allergies in Childhood 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% (95% CI, 1.6% to 2.3%), egg allergy was 1.2% (95% CI, 0.9% to 1.6%), and sesame allergy was 0.4% (95% CI, 0.3% to 0.6%). Late-onset peanut allergy at age 4 years was rare (0.2%). The prevalence of current asthma was 10.8% (95% CI, 9.7% to 12.1%), current eczema was 16.0% (95% CI, 14.7% to 17.4%), and current allergic rhinitis was 8.3% (95% CI, 7.2% to 9.4%). Forty percent to 50% of this population-based cohort experienced symptoms of an allergic disease in the first 4 years of their life.

Conclusions: Although the prevalence of food allergy decreased between age 1 year and age 4 years in this population-based cohort, the prevalence of any allergic disease among 4-year-old children in Melbourne, Australia, is remarkably high. (J Allergy Clin Immunol 2017;140:145-53.)

Key words: *Allergy, asthma, eczema, egg allergy, food allergy, allergic rhinitis, HealthNuts, longitudinal study, peanut allergy, prevalence, population-based study, sesame allergy*

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 recognized as a significant public health concern in many developed countries.

Until recently, the prevalence of food allergy has been difficult to estimate because of 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

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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. K.J.A., L.C.G., A.J.L., M.W., J.J.K., and S.C.D. hold NHMRC awards.

Disclosure of potential conflict of interest: M. Wake receives grant support from the National Health and Medical Research Council (NHMRC), the Australian National Health & Medical Research Council, and the Foundation for Children; serves as a consultant for Longitudinal Study of Australian Children; received payment for lectures from Sandoz; and received travel support from Victorian State Government, Australia. A.-L. Ponsonby receives grant support from the NHMRC. M. L. K. Tang serves on the board for Nestle Nutrition Institute and Danone Nutricia; serves as a consultant for GLG Consultant and DeerField; received payments for lectures from Danone Nutricia and MD Linx; holds patents with Murdoch Childrens Research Institute; and receives royalties from Wiley. A. J. Lowe receives grant support from the NHMRC. K. J. Allen serves as a consultant for Nestle, ThermoFisher, AspenCare, Before Brands, and Nutricia. The rest of the authors declare that they have no relevant conflicts of interest.

Received for publication September 26, 2016; revised January 31, 2017; accepted for publication February 3, 2017.

Available online May 14, 2017.

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0091-6749/$36.00

http://dx.doi.org/10.1016/j.jaci.2017.02.019

Abbreviations used
ISAAC: International Study of Asthma and Allergies in Childhood
OFC: Oral food challenge
sIgE: Specific IgE
SPT: Skin prick test

on self-report or measures of sensitization, 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 were 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 twelve-month-old infants were recruited (74% participation) from council-run immunization sessions where they underwent SPT screening to 4 common food allergens: egg, peanut, sesame, and either cow's milk or shrimp. Any infant with a detectable SPT wheal (≥1 mm) 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 (sIgE) (both of which were used to define sensitization status). If SPT result was negative (0 mm) at community recruitment, infants were considered to be food tolerant. To test this assumption, a random sample of 200 infants (SPT wheal 0 mm) underwent OFC to egg or peanut and all were tolerant.

Age 4-year follow-up. The first longitudinal follow-up on the entire cohort was undertaken in the child's fourth year, as previously described.[12] Parents were mailed a questionnaire that 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 International Study of Asthma and Allergies in Childhood (ISAAC). 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 that 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 year 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 year, they underwent repeat OFC at age 4 years 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 year and those who reported symptoms of a new food allergy initially underwent SPT. If SPT demonstrated evidence of sensitization and there was no 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]

SPTs and serum sIgE. 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 clinical history.[13,14] Criteria for a positive OFC were more than 3 noncontact 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) is included in this article's Online Repository at www.jacionline.org.

Definitions for age 1-year allergy outcomes. *Challenge-confirmed food allergy:* Positive OFC (or recent reaction consistent with OFC-stopping criteria) and positive test of sensitization (SPT wheal ≥ 2 mm and/or sIgE ≥ 0.35 kU/L).

Food tolerance: Negative OFC or SPT wheal 0 mm 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-year allergy outcomes. *Challenge-confirmed food allergy:* Positive OFC (or recent reaction consistent with OFC-stopping criteria) and positive test of sensitization (SPT wheal ≥ 3 mm and/or sIgE ≥ 0.35 kU/L).

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

Probable and possible food allergy and tolerance: Participants who were eligible for but declined a food challenge were assigned a probable or possible food allergy status on the basis of SPT responses and/or clinical history (for full definitions, see this article's Methods section and Fig E1 in the Online Repository at www.jacionline.org).

The definitions for other allergic outcomes obtained from the full questionnaire, using the ISAAC questions, are as follows (for a full list of questions and definitions, see Table E2 in this article's Online Repository at www.jacionline.org).

Parent-report asthma ever: Parent report of asthma ever.

Doctor-diagnosed asthma ever: 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.

Doctor-diagnosed eczema 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, for example, 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.