

Letter to the Editor

No cashew allergy in infants introduced to cashew by age 1 year*To the Editor:*

Similar to peanut allergy, tree nut allergy is common, can be severe, and seldom resolves.^{1,2} Evidence that early introduction of peanut and egg before age 12 months reduces the prevalence of IgE-mediated food allergy has led to a paradigm shift in infant feeding advice for allergenic solid foods, from avoidance to timely introduction.³ In recent years, infant feeding guidelines internationally recommend introduction of allergenic foods such as peanut in the first year of life; however, because of lack of evidence, there was no specific recommendation for tree nut introduction.^{4,5} We aimed to determine whether the introduction of cashew in the infant diet in the first year of life was associated with the risk of cashew allergy.

HealthNuts is a population-based longitudinal study of 5276 infants recruited from council-run immunization sessions in metropolitan Melbourne, Australia, at age 11 to 15 months from 2007 to 2011. Parents completed a questionnaire collecting demographic information as well as data on the timing of food introduction in the infant's diet; specifically, parents were asked whether they had introduced any nuts into the infant's diet, to specify which nut and the age in months that the nut had been introduced. Skin prick testing (SPT) at recruitment was performed to 4 foods (milk, egg, peanut, and sesame), and infants with a detectable wheal (≥ 1 mm) were invited for oral food challenge (OFC) at the Royal Children's Hospital, Melbourne, Australia. OFCs were deemed positive if they met 1 of the following criteria, 3 or more noncontact urticaria lasting for 5 minutes or more, angioedema, vomiting, or evidence of anaphylaxis. The cohort was followed up at age 4 years with a questionnaire and those who reported any new food reactions or who were food allergic at age 1 year were invited for an allergy assessment that included a panel of SPT (including cashew) and OFC. Cashew OFCs were first performed at age 4 years among those with detectable cashew wheal but no known tolerance. The first comprehensive assessment of cashew allergy prevalence was undertaken at age 6 years, where all participants were invited to complete a questionnaire and comprehensive health assessment that included SPT to 8 foods including cashew. Those with a detectable SPT wheal (≥ 1 mm) were offered OFC.⁶ Cashew sensitization at age 6 years was defined as SPT wheal size greater than or equal to 3 mm. Cashew allergy at age 6 years was defined as previously described and was informed by OFC, SPT, and questionnaire responses (see footnote Table 1).¹ Timing of cashew introduction was dichotomized as early (age ≤ 12 months) or delayed (age > 12 months or not yet introduced).

The association between introduction of cashew and cashew sensitization was modeled using logistic regression; exact logistic regression was used for cashew allergy because 1 of the cells formed by the outcome and categorical predictor variable had no observations.⁷ Potential confounders considered were sex, parental country of birth (both Australia, 1 or both Asian and other), presence of siblings, pet dogs (none, allowed inside the house, outside only), parent report of a doctor diagnosis of

eczema, parent-reported reactions to common food allergens, sibling history of allergy (no siblings, siblings without allergy, siblings with allergy), and family history of allergy, all reported in the age 1 year questionnaire. All statistical analysis was performed using Stata (Release 15.1; StataCorp LLC, College Station, Tex). Ethics approval was obtained from the Royal Children's Hospital Human Research Ethics Committee (27047 and 32294) and from the Victorian State Government Office for Children (CDF/07/492) and the Department of Human Services (10/07).

As described previously,^{1,6} the participation rate in the HealthNuts study was 74% ($n = 5276$) at age 1 year, whereas at age 6 years, 84% ($n = 4441$) of the original cohort completed a questionnaire and 61% ($n = 3232$) completed a health assessment. The present analysis includes participants with complete data on age of introduction of cashew reported at age 1 year, potential confounders considered, and cashew allergy outcomes ($n = 2925$ for cashew allergy and $n = 2539$ for cashew sensitization). By age 12 months, 4.8% ($N = 140$ of 2925; 95% CI, 4.0%-5.6%) of infants had consumed cashew. At age 6 years, the prevalence of cashew sensitization was 4.8% (95% CI, 4.0%-5.7%) and that of cashew allergy was 3.4% (95% CI, 2.8%-4.1%). These estimates differ from the estimates from previous reports from our cohort because it is restricted to those who had complete data for this analysis. No child who ate cashew by age 12 months developed cashew allergy (0%; 95% CI, 0%-2.6%), compared with 3.6% (95% CI, 2.9%-4.4%) of those who had not consumed cashew by age 12 months. After adjustment for confounding variables, there was weak evidence that early introduction of cashew was associated with reduced odds of cashew allergy (adjusted odd ratio, 0.19; 95% CI, 0.00-1.09; $P = .07$). The magnitude of association was similar for cashew sensitization, but CIs were wider (adjusted odds ratio, 0.22; 95% CI, 0.03-1.61; $P = .14$).

This is the first report of a possible protective association between the ingestion of cashew in the first year of life and cashew allergy. In 2015, the Learning Early About Peanut randomized controlled trial showed that in a cohort with severe eczema or egg allergy ($n = 628$), regular ingestion of peanut up to age 60 months reduced peanut allergy by 81%, compared with the control group who avoided peanut for this time (17.2% to 3.2%; $P < .01$).⁸ It has been postulated that the high-risk cohort of Learning Early About Peanut and the extended length of allergen avoidance in the control group may overstate the true population effect of early peanut introduction, although interestingly, our observational population-based study has found a similar reduction in risk for early cashew introduction. The dual allergen exposure hypothesis described by Lack⁹ is a plausible explanation for these results.

Strengths of our study include the population-based rather than high-risk cohort, with findings generalizable to the wider population. Furthermore, the HealthNuts study uses definitive allergy outcomes, including OFCs to define food allergy prevalence. Limitations include the possibility of recall error for early life exposures that were reported at age 1 year; however, because these were completed at age 12 months, information on whether or not food allergens had been introduced is likely to be reliable. Selective attrition may have increased the prevalence of cashew allergy at age 6 years, due to higher rates of participation by those with a family or personal history of allergy, but this is unlikely to

TABLE I. Association between age of cashew ingestion and cashew allergy outcomes at age 6 y

Outcome	N*	%	Unadjusted OR (95% CI)	P value	Adjusted OR† (95% CI)	P value
Cashew sensitization						
Delayed	2427	4.94	Reference group	—	Reference group	—
Early	112	0.89	0.17 (0.02-1.25)	.08	0.22 (0.03-1.61)	.14
Cashew allergy‡						
Delayed	2785	3.59	Reference group	—	Reference group	—
Early	140	0.00	0.13 (0.00-0.73)	.01	0.19 (0.00-1.09)	.07

OR, Odds ratio.

*Only participants with complete data on exposure, outcomes, and potential confounders contributed data to this table. The sample size for cashew allergy is greater than that for cashew sensitization, because cashew tolerance was informed by questionnaire data for those who did participate in SPT.

†The cashew sensitization model was adjusted for patient sex, parental country of birth, pet dogs, siblings, family history of any allergy, sibling history of allergy, eczema diagnosis, and parent-reported reaction to foods. Because of computational limitations of running exact logistic regression models, only a limited number of confounders could be adjusted for simultaneously. Separate models were run adjusting for each potential confounder individually, with the final model adjusted for the only 2 variables that altered the magnitude of association from the unadjusted OR: parent-reported reaction to common allergens and parent-reported eczema diagnosis.

‡Cashew allergy was defined as any of the following in the context of cashew sensitization: (1) positive OFC (n = 21), (2) recent reaction consistent with OFC stopping criteria in the past 12 mo (n = 5) or (3) positive OFC at age 4 y with SPT ≥8 mm at age 6 y (n = 32), or (4) SPT response of ≥8 mm but no age 4 y OFC (n = 42). Cashew tolerance was defined as any of the following: (1) negative OFC; (2) SPT response of 0-2 mm; (3) SPT response of 3-7 mm or no SPT, and parent-reported ingestion history (eaten >1 time since age 4 y) and no reaction since age 4 y and no parental report of food avoidance.¹

have biased the association between age of introduction and cashew allergy.¹

We present the first evidence that the early introduction of cashew may decrease the frequency of cashew allergy in a population-based cohort; however, cashew allergy and introduction was uncommon and the risk reduction could not be quantified precisely. Future clinical trials are required to assess the frequency, dose, and timing of cashew ingestion for cashew allergy prevention, and how cashew can be safely and effectively introduced with other allergenic solid foods into the infant's diet, which may be key to reversing the food allergy epidemic.

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Rachel L. Peters, PhD^{a,b}

Danny Ye Barret, MD^{a,b}

Victoria X. Soriano, BSc (Hons)^{a,b}

Vicki McWilliam, PhD^{a,c}

Adrian J. Lowe, PhD^{a,d}

Anne-Louise Ponsonby, PhD^{a,e}

Mimi L. K. Tang, MD, PhD^{a,b,c}

Shyamali C. Dharmage, PhD^{a,d}

Lyle C. Gurrin, PhD^d

Jennifer J. Koplin, PhD^{a,b,*}

Kirsten P. Perrett, MD, PhD^{a,b,c,*}

From ^aMurdoch Children's Research Institute, ^bthe Department of Paediatrics, The University of Melbourne, ^cthe Department of Allergy and Immunology, Royal Children's Hospital, ^dthe School of Population and Global Health, The University of Melbourne, and ^eThe Florey Institute, Parkville, Australia. E-mail: kirsten.perrett@rch.org.au.

*Equal senior author.

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