

REVIEWER COMMENTS. Recent studies have demonstrated that sensitization and clinical reactions to eggs can occur early in susceptible individuals, often with reactions occurring at the first exposure to egg. Like the LEAP study for peanut, it would be helpful to be able to use early introduction of egg to promote the development of oral tolerance instead of food allergy. This is the first randomized controlled study to show that increasing amounts of egg in a maternal diet are associated with more egg in breast milk. Infant IgG4 levels also increase proportionally, possibly supporting the development of early oral tolerance.

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### Clinical Features of Food Allergy During the First Year of Life: The ADAPAR Birth Cohort Study

Doğruel D, Bingöl G, Altıntaş DU, Yılmaz M, Güneşer Kendirli S. *Int Arch Allergy Immunol*. 2016;169(3):171–180

PURPOSE OF THE STUDY. To assess the incidence of food allergies and identify risk factors for the development of food allergies in infants.

STUDY POPULATION. The study population was part of the Adana Pediatric Allergy and Risk Factor (ADAPAR) birth cohort study in Adana, Turkey. From February 2010 to February 2011, 1475 infants born at a single center were enrolled. Infants were followed from birth until 1 year of age.

METHODS. At birth, umbilical cord blood was collected, and infants were examined. The infants returned for study visits at 3, 6, and 12 months of age. The subjects' mothers completed questionnaires at birth, at each study visit, and over the phone at 9 months. Skin prick testing (SPT) and serum-specific IgE levels (SSiGE) (cow's milk, hen's egg, soy, wheat, fish, and peanuts) were measured at 6 and 12 months of age. Additional testing was done at 3 and 9 months when there was suspicion of allergic disease. Food allergy (based on clinical history, positive SPT, or positive SSiGE) was confirmed with standardized oral food challenge (OFC).

RESULTS. Of the 1475 study subjects recruited at birth, 1377 infants were enrolled, and 920 had available SSiGE and/or SPT results. While 90 infants (6.5%) were noted to have reactions suspicious for food allergy, a diagnosis of food allergy was confirmed in 33 of 1377 infants (2.4%). Thirty-two of the 33 infants had a positive OFC, and 1 infant had a clinical history consistent with anaphylaxis to milk. The most frequent symptoms reported during OFC were cutaneous (74%,  $n = 28$ ) and gastrointestinal (18%,  $n = 7$ ). The most common allergens confirmed by OFC were milk (51.3%,  $n = 20$ )

and egg (43.7%,  $n = 17$ ). Infants with confirmed food allergy were significantly more likely to have the following characteristics compared with infants without food allergies: male sex, atopic dermatitis, history of wheezing, and family history of atopy. Multivariate regression analysis showed that having a food-allergic sibling significantly increased the risk for food allergy (OR 18.9, 95% CI 1.59–224.05).

CONCLUSIONS. Food allergy was confirmed in 33 (2.4%) of these infants. The most common food allergy was milk followed by egg, and the most frequent symptom during a positive food challenge was cutaneous. A sibling with food allergy was a significant risk factor for the development of food allergies in infancy.

REVIEWER COMMENTS. This study adds further insight into the characteristics of food allergy in infants with milk and egg allergy being diagnosed as early as 3 to 4 months of age. Worsening eczema was included as an indicator of a positive food challenge; however, it is unclear if eczema was measured objectively, and thus, true IgE-mediated allergy to food may have been overestimated. The timing of food allergy onset is of interest in the setting of an increasing focus on food allergy prevention by intervening during infancy.

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### Food Allergy Sensitization and Presentation in Siblings of Food-Allergic Children

Gupta RS, Walkner MM, Greenhawt M, et al. *J Allergy Clin Immunol Pract*. 2016;4(5):956–962

PURPOSE OF THE STUDY. To determine the prevalence of food sensitization and clinical food allergy among siblings of food-allergic children.

STUDY POPULATION. Children were enrolled as part of the Chicago Family Cohort Food Allergy study. Eligible families had 1 index child with confirmed food allergy and at least 1 sibling participating in the study. There were 478 food-allergic children and 642 siblings. Of index children, 63.6% were male, and 50% were between the ages of 2 and 5 years. Of siblings, 66.5% were younger than the index child.

METHODS. A structured questionnaire-based interview was performed with each parent. Serum IgE (sIgE) values for 9 common food allergens (egg white, sesame, peanut, soy, cow milk, shrimp, walnut, codfish, and wheat) were measured for each subject. sIgE values  $\geq 0.35$  KU/L were considered positive. Serum prick tests (SPT) were performed for the same food allergens, with fish mix and shellfish mix used instead of codfish and shrimp. A mean wheal diameter 3 mm greater than the saline control was considered

positive. Oral food challenges were not performed. Stringent clinical criteria indicative of highly likely clinical food allergy were met if a subject had evidence of sensitization and a reported history of symptoms of an allergic reaction to a food within 2 hours of ingestion.

**RESULTS.** Among siblings of food-allergic children, 13.6% had clinical food allergy, most commonly to milk (5.9%), followed by egg (4.4%) and peanut (3.7%). The prevalence of sensitization to any food without clinical allergy was 53%, while 33.4% of participants had neither sensitization nor clinical allergy. The most common sensitizing foods were wheat (36.5%), followed by milk (35.4%) and egg (35.1%). Risk factors associated with the development of clinical food allergy in siblings included a history of asthma (RRR 4.14; 95% CI, 2.04–8.59;  $P < .01$ ) and eczema (RRR 3.60; 95% CI, 2.04–6.34;  $P < .01$ ). Furthermore, eczema was significantly associated with sensitization (RRR 1.66; 95% CI, 1.12–2.45,  $P < .05$ )

**CONCLUSIONS.** Although 13.6% of siblings of food-allergic children had a clinically reactive food allergy, the majority (53%) were sensitized to food but did not have clinical food allergy.

**REVIEWER COMMENTS.** Parents of food-allergic children are often concerned about the presence of food allergy in the children's siblings and seek testing. This study demonstrated that the risk of clinical food allergy is only slightly higher in siblings of food-allergic children (1 in 8) compared with the general population (1 in 12). On the other hand, the rate of asymptomatic sensitization without clinical food allergy is high. Therefore, screening siblings for food allergy is likely to result in a high rate of misdiagnosis and unnecessary dietary restriction, potentially leading to adverse outcomes. These findings are in agreement with the NIAID food allergy guidelines, which do not recommend screening siblings of food-allergic children. In specific situations, such as in the case of parents who express marked anxiety about introducing allergenic foods to the siblings, skin testing and/or sIgE testing for foods may be performed with the understanding that an oral food challenge may be needed to confirm clinical allergy when sensitization is demonstrated.

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### **The Component-Specific to Total IgE Ratios Do Not Improve Peanut and Hazelnut Allergy Diagnoses**

Grabenhenrich L, Lange L, Härtl M, et al. *J Allergy Clin Immunol.* 2016;137(6):1751–1760.e8

**PURPOSE OF THE STUDY.** Food challenge remains the gold standard for diagnosing food allergy. Developing alternative tests

with improved ability to predict outcomes of food challenges has been elusive. Determining the sensitization to individual proteins, known as component-resolved diagnosis (CRD), has improved models predicting outcomes of food challenges to peanut (Ara h 2-specific IgE) and hazelnut (Cor a 14-specific IgE). The ratio of whole allergen-specific IgE to total IgE has also been investigated for predicting food challenge outcomes. This study aim was to see if the ratio of specific-component IgE to total IgE can improve the prediction of food challenge outcomes.

**STUDY POPULATION.** Children referred to 9 pediatric allergy clinics across Germany for a first evaluation of peanut allergy, hazelnut allergy, or both were eligible. Children included were those who were sensitized to peanut or hazelnut but had no history of exposure or those who had a recent immediate food reaction wherein peanut or hazelnut was the suspected causative agent.

**METHODS.** Blood samples were collected from participants. In suspected peanut allergy cases, specific-IgE levels against whole peanut and 4 peanut proteins (Ara h 1, Ara h 2, Ara h 3, and Ara h 8) were measured, and for suspected hazelnut allergy cases, IgE levels against whole hazelnut and 4 hazelnut proteins (Cor a 1, Cor a 8, Cor a 9, and Cor a 14) were measured. Levels were determined by using the ImmunoCAP-FEIA method. Food challenges were conducted in all participants to diagnose food allergy. Ratios of specific to total IgE were compared with raw IgE levels in terms of discrimination and prediction.

**RESULTS.** Forty-three percent of 207 children with suspected peanut allergy and 31% of 142 children with suspected hazelnut allergy were confirmed as having food allergy by a positive food challenge. There was not a significant difference between the performance measures for Ara h 2-specific IgE versus the ratio of Ara h 2-specific to total IgE (area under the curve 0.93 vs 0.92). There was also no significant difference between the performance measures for Cor a 14-specific IgE versus the ratio of Cor a 14-specific to total IgE (area under the curve 0.89 vs 0.87). The probability of positive peanut challenge with an Ara h 2-specific IgE of 0.35 kU/L was 16% when the total IgE level was >500 kU/L, compared with 48% for IgE levels of 100 to 500 kU/L and 51% for IgE levels of <100 kU/L. At a Cor a 14-specific IgE level of 0.35 kU/L, a positive food challenge was seen 7% of the time with total IgE being >500 kU/L, compared with 32% with total IgE of 100 to 500 and 34% with total IgE being <100.

**CONCLUSIONS.** Using a ratio of component-specific IgE to total IgE for peanut and hazelnut did not improve performance in predicting food allergy compared with using the specific-component levels alone. Higher total IgE levels might indicate lower probabilities of reaction at a given component-specific IgE level.

## Food Allergy Sensitization and Presentation in Siblings of Food-Allergic Children

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