

**STUDY POPULATION.** Patients were recruited at Ryugasaki Saiseikai Hospital in Japan. The study included 51 children with IgE-CMA (defined as having had immediate allergic reactions within 2 hours of ingestion, a CM IgE level  $\geq 0.7$  kU<sub>A</sub>/L, and diagnosis by a board-certified allergy specialist) and 102 age- and sex-matched controls seen for the common cold or routine vaccination without having a CMA or other food allergy. An additional 32 unmatched patients with an IgE-mediated egg allergy (egg-IgE  $> 0.7$  kU<sub>A</sub>/L and diagnosis by a specialist) and without a milk-related food allergy were also included. All patients were older than 1 year of age at the time of enrollment.

**METHODS.** This was a retrospective case-control study of pediatric patients recruited from November 2014 to February 2015. A standardized questionnaire was completed by the parents and included information regarding past histories of allergic diseases, family history of allergic diseases, time of introduction of nonregular (not used daily) CM formula, time of introduction of regular (used daily) CM formula, feeding patterns in the first month of life and reason for choosing those patterns, and timing of discontinuation of CM formula and reason for discontinuation. Feeding patterns in the first month of life were categorized as (1) exclusive breastfeeding with no formula; (2) almost exclusive breastfeeding with CM formula less than daily; (3) mixed, feeding predominantly with breast milk but with CM formula at least once a day; (4) mixed, feeding predominantly with CM formula; and (5) exclusive CM formula and no breast milk.

**RESULTS.** The rates of atopic dermatitis and bronchial asthma were significantly higher in the CMA group ( $P < .001$  and  $P = .12$ , respectively). The CMA group also showed increased maternal age at delivery, paternal asthma, paternal rhinitis, maternal asthma, maternal food allergy, and decreased pet ownership ( $P < .05$ ). Compared with the egg-allergic group, the CMA group showed significantly higher rhinitis and maternal asthma ( $P < .05$ ). Exclusive breastfeeding was significantly higher in the CMA group, whereas early regular CM formula feeding (once daily within the first month of life) and early regular continuous CM formula feeding (once daily within the first month of life and continued until 6 months or until the onset of CMA) were significantly higher in the controls. In a multivariable logistic regression analysis that controlled for allergic symptoms, parental age at delivery, and family history of allergic diseases, the adjusted odds ratio of delayed (started 1 month after birth) or no cow's milk formula (less than once daily) was 23.74 (95% CI, 5.39–104.52) for the CMA group compared with the controls and 10.16 (95% CI, 2.48–41.64) compared with the egg-allergic group. The odds ratio of CMA versus control was even higher when looking at no early regular continuous CM formula feeding (92.76 [95% CI, 9.05–951.04]).

**CONCLUSIONS.** Early (starting in the first month of life) and regular (daily) exposure to CM is protective against the development of IgE-mediated CMA.

**REVIEWER COMMENTS.** This relatively small study supports the hypothesis that early ingestion of an allergen may be protective against the development of a food allergy. The general notion is supportive of a previous study on the early introduction of peanuts to prevent peanut allergy, although that trial introduced peanuts at 4 up to 11 months of age (Du Toit G et al, *N Engl J Med.* 2015;372 [9]:803–813). There are limitations to this current study. The study was retrospective, and maternal recall can be inaccurate. The study does not delineate the time after initial exposure to regular ingestion of CM formula nor the amounts ingested. There may be an optimal time from initial exposure to regular introduction. A study by Katz Y et al (*J Allergy Clin Immunol.* 2010;126[1]:77–82) noted a window during which early regular consumption (in the first 14 days) was protective of IgE-CMA, but rates were also lower for any age other than introduction from 105–194 days. Randomized trials will be needed to better understand the role of very early introduction of CM, especially as this broaches the topic of exclusive breastfeeding.

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### **Two-step Egg Introduction for Prevention of Egg Allergy in High-risk Infants With Eczema (PETIT): A Randomized, Double-blind, Placebo-Controlled Trial**

Natsume O, Kabashima S, Nakazato J, et al. *Lancet.* 2017; 389(10066):276–286

**PURPOSE OF THE STUDY.** The Prevention of Egg Allergy with Tiny Amount Intake is a double-blind, placebo-controlled trial that investigated the stepwise introduction of hen's egg and the optimal eczema treatment for preventing an egg allergy at the age of 1 year.

**STUDY POPULATION.** Healthy Japanese infants with eczema and without previous ingestion of or reactions to hen's egg ( $N = 147$ ) were randomized (1:1, stratified by institution and sex) at the ages of 4–5 months to consume either egg or a placebo.

**METHODS.** Infants in the egg group consumed 50 mg of heated egg powder per day from ages 6–9 months and consumed 250 mg per day from ages 9–12 months. Infants in the placebo group consumed squash powder with matched color and volume. At the age of 12 months, the proportion of infants with an egg allergy in each group was confirmed by open food challenges to 7 g of egg powder. Sensitization to egg was measured by egg-

specific IgE level (sIgE), and eczema was assessed by Scoring Atopic Dermatitis (SCORAD) severity score.

**RESULTS.** The study was terminated when the interim analysis showed a protective effect of egg ingestion. Among infants completing the open egg challenge ( $N = 121$ ), 5 (8%) had an egg allergy in the egg group versus 23 (38%) in the placebo group (risk ratio 0.221 [95% CI 0.090–0.543],  $P = .0001$ ). In stratified analyses, egg ingestion was protective for egg-sensitized infants (sIgE  $\geq 0.35$  kUA/L,  $P = .001$ ) but not for nonsensitized infants (sIgE  $< 0.35$  kUA/L,  $P = .31$ ).

**CONCLUSIONS.** Daily consumption of a small amount of egg and aggressive eczema care starting at age 6 months prevents egg allergy in high-risk infants at age 12 months.

**REVIEWER COMMENTS.** This stepwise egg introduction to infants with eczema appeared to be safe; no severe, immediate allergic reactions were reported at home, although anaphylaxis occurred during some monitored egg challenges. The significantly higher baseline egg sensitization rate and SCORAD in the placebo group were important limitations that may have affected the rates of egg allergy in the 2 groups and biased the results. The median baseline SCORAD was in the moderate range for the placebo group and in the mild range for the egg group; eczema was well controlled with minimal topical steroid use, suggesting that few infants had severe or difficult-to-control eczema.

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### Timing of Allergenic Food Introduction to the Infant Diet and Risk of Allergic or Autoimmune Disease: A Systematic Review and Meta-analysis

Lerodiakokonou D, Garcia-Larsen V, Logan A, et al. *JAMA*. 2016;316(11):1181–1192

**PURPOSE OF THE STUDY.** To determine whether the timing of allergenic food introduction influences the risk of development of allergic or autoimmune disease.

**STUDY POPULATION.** Meta-analysis of studies evaluating the timing of allergenic food introduction in the first year of life and reported allergy, allergic sensitization, or autoimmune disease.

**METHODS.** A comprehensive literature search from January 1, 1946, to March 8, 2016, was performed. Participants were enrolled within 6 months of life, and outcomes were evaluated between 7 months and 6 years of age. Across the 146 studies evaluated, the age of allergenic food introduction and associated allergic or autoimmune outcomes were compared in 24 interventional/69 observational studies and in 6 interventional/48 observational studies, respectively. Bias and statistical heterogeneity were quantified by using validated methodology. A post hoc trial

sequential analysis quantified the statistical reliability of the moderate- to high-certainty findings with egg introduction and gluten introduction. The certainty of evidence score was determined by using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system.

**RESULTS.** The meta-analysis of 5 trials with 1915 participants found a decreased risk of developing an egg allergy with egg introduction at 4 to 6 months (RR 0.56; 95% CI, 0.36–0.87). Meta-analysis of 2 trials with 1550 participants found a lower risk of developing a peanut allergy when peanut was introduced at age 4 to 11 months (RR 0.29; 95% CI, 0.11–0.74). There was no association with the timing of introduction of other allergenic foods (milk, wheat, soy, tree nuts, and shellfish) and the risk of allergic sensitization or food allergy. There was conflicting evidence about the early introduction of fish and the associated risk of allergic sensitization. No association was found between the timing of gluten introduction and celiac disease, inflammatory bowel disease, or type I diabetes mellitus or between the timing of milk introduction and type 1 diabetes mellitus.

**CONCLUSIONS.** There is moderate-certainty evidence that the introduction of egg between 4–6 months of age and peanut between 4–11 months of age is associated with a reduced risk of egg and peanut allergy, respectively. There is low- to very-low-certainty evidence that fish introduction between 6–12 months of age is associated with decreased allergic sensitization or rhinitis. There is high-certainty evidence that the timing of gluten introduction has no association with celiac disease.

**REVIEWER COMMENTS.** This large-scale meta-analysis and systematic review concludes that the early ingestion of egg and peanut is associated with antigen-specific oral tolerance, a heartening finding with significant implications for families wondering about the right age to introduce these potentially allergenic foods. There was no consistent evidence, however, that the introduction of 1 food influences the development of a different food allergy. Reassuringly, there was no consistent evidence that the timing of food introduction impacts autoimmune diseases, including celiac disease, type I diabetes mellitus, or inflammatory bowel disease.

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### Parental Timing of Allergenic Food Introduction in Urban and Suburban Populations

Hartman H, Dodd C, Rao M, et al. *Ann Allergy Asthma Immunol*. 2016;117(1):56–60

**PURPOSE OF THE STUDY.** To investigate the differences in early food introduction in urban versus suburban populations.

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