with no significant differences in immunoglobulin E, AD, wheeze, or sensitization to food or aeroallergens. The cohort studies of maternal fish intake also found no effect on odds ratios for rates of sensitization, AD, AR, wheeze, or asthma. High fish intake during infancy was associated with a 39% reduction in eczema and a 46% reduction in AR. A borderline association with sensitization was found at 4 years of age but was lost by 8 years. No effect was found on wheeze or asthma. There was no study in which researchers reported an association between fish intake during pregnancy or infancy with food allergy.

CONCLUSIONS. Fish intake during infancy is associated with a lower risk of AR and eczema, whereas maternal intake of fish during pregnancy is not.

REVIEWER COMMENTS. Oily fish are a rich source of n-3 long-chain polyunsaturated fatty acids such as docosahexaenoic acid and eicosapentaenoic acid, which have been suggested to lower the risk of allergic disease through anti-inflammatory effects. The mechanism underlying the association between fish intake in infancy and lower risk of AR and AD remains unclear. Furthermore, the findings of this meta-analysis are potentially limited by publication bias and reverse causation (avoidance of fish because of early signs of atopy). Current expert recommendations are to introduce solid foods beginning at 4 to 6 months of age without delaying the introduction of highly allergenic foods, such as fish.

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Prenatal Fish Oil Supplementation and Allergy: 6-Year Follow-up of a Randomized Controlled Trial

Best KP, Sullivan T, Palmer D, et al. *Pediatrics*. 2016; 137(6):e20154443

PURPOSE OF THE STUDY. To assess whether prenatal supplementation with ω-3 (n-3) long-chain polyunsaturated fatty acids (LCPUFA) exerts a protective effect on the development of immunoglobulin E–mediated allergic conditions at 6 years of age in a prospective birth cohort.

STUDY POPULATION. A total of 706 children with a family history of allergic disease were enrolled into this study as part of the Docosahexaenoic Acid to Optimize Mother Infant Outcome trial.

METHODS. Women with a singleton pregnancy (<21 weeks' gestation) were recruited from the Docosahexaenoic Acid to Optimize Mother Infant Outcome randomized controlled trial (RCT) during an antenatal clinic visit. Participants were randomly assigned in a double-blind manner to receive either 500 mg of fish oil concentrate (~800 mg/day docosahexaenoic acid and 100 mg/day eicosapentaenoic acid) or 500 mg of vegetable oil from 21 weeks' gestation until delivery. Women were eligible to enroll in the follow-up study if their unborn children had a family history of atopic disease. Eligible offspring were evaluated in person at age 6 years for allergic disease via a validated questionnaire (International Study of Asthma and Allergies in Childhood), which assessed symptoms experienced over the previous 12 months and included skin prick testing for common food and environmental aeroallergens.

RESULTS. A total of 668 participants from the initial cohort were eligible for the follow-up study. Participant demographics were similar between the 2 groups. Seventy percent of participants had a history of maternal allergic disease compared with 54% who had a history of paternal allergic disease; 24% had a history of atopic disease in both parents. There were no significant differences in the reporting of allergic disease (eczema, wheeze, or rhinitis) on a symptom-based questionnaire between the n-3 LCPUFA and control groups. Rhinitis was the most common symptom (31.5%) affecting the birth cohort. There was also no difference between the groups in percent sensitized to at least 1 allergen on skin prick testing. The only minor difference was a reduction in the percentage sensitized to 1 of the common house dust mite allergens, *Dermatophagoides farinae* (13.4% vs 20.3%; adjusted relative risk, 0.67; 95% confidence interval, 0.44–1.00; $P = .0495$), in the intervention group.

CONCLUSIONS. Prenatal supplementation with n-3 LCPUFA did not reduce the development of allergic disease or sensitization in participants with a family history of atopy compared with control participants at the 6-year follow-up evaluation.

REVIEWER COMMENTS. The quest to find a prenatal intervention that effectively prevents the development of allergic conditions in children continues. To date, this study is the largest RCT in which the researchers assessed the prenatal effect of fish oil supplementation. One of the strengths of the study includes its large sample size and high retention rate. However, no significant differences in primary clinical outcomes of eczema, wheeze, or rhinitis were detected, which is in contrast to previous RCTs, which vary in methodology and age at follow-up. Challenges from similar prenatal interventional studies arise from determining the type of intervention (n-3 fatty acids, vitamin D, probiotics, and prebiotics), the timing and duration of intervention, and what type of product and dosing to use. Although prenatal interventions such as these generally offer little risk to mother or infant, further studies are warranted

to determine efficacy in preventing sensitization and progression to clinical disease.

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Serum 25-Hydroxyvitamin D in Early Childhood Is Nonlinearly Associated With Allergy

Savilahti EM, Mäkitie O, Kukkonen AK, et al. *Int Arch Allergy Immunol*. 2016;170(3):141–148

PURPOSE OF THE STUDY. To assess for an association between serum 25-hydroxyvitamin D (25-OHD) levels at birth and at 2 years of age and the development of allergic sensitization and disorders in early childhood.

STUDY POPULATION. Subjects were part of a randomized, double-blinded, placebo-controlled trial designed to evaluate the effect of probiotics on allergy development. Infants with family history of atopy (1 or both parents had doctor-diagnosed allergic disease) were managed from birth until 5 years of age (n = 819).

METHODS. Subjects were examined at 3 months, 6 months, 2 years, and 5 years of age. The primary outcome was the cumulative incidence of any allergic disease and any immunoglobulin E (IgE)–mediated allergic disease until the age of 2 or 5 years. Skin prick tests and serum-specific IgE to a panel of foods and environmental aeroallergens were completed at 2 and 5 years. Sensitization was defined as at least 1 or more positive skin prick test (≥3 mm larger than negative control) results or positive serum-specific IgE (>0.7 kU/L) results. IgE-mediated allergy was defined as sensitization that matched the allergic disorder. 25-OHD levels were measured from cord blood at birth (divided into tertiles) and serum at 2 years of age (divided into quartiles). The following variables were included in the multivariate logistic regression if they met the criteria for confounding: sex, dual parental allergy, mode of delivery, season of birth, season when 2-year serum sample was drawn, months of exclusive breastfeeding, household smoking (at age 0–2 years), and having a cat or dog in the household (at age 0–2 years). Probiotic treatment group was included in all regression models.

RESULTS. Cord blood 25-OHD levels in the second tertile (21.5–29.5 nmol/L) were significantly associated with increased allergic sensitization by 2 years of age (odds ratio [OR] 1.59; 95% confidence interval [CI]: 1.06–2.39) and allergic disorders by 5 years (OR 1.85; 95% CI: 1.25–2.73). 25-OHD levels measured at 2 years of age in the third quartile (51.7–62.6 nmol/L) were significantly associated with increased allergic sensitization by 5 years (OR 2.23; 95% CI: 1.21–4.12), increased diagnosis of IgE-associated allergic disorder by 5 years (OR 2.35; 95% CI: 1.22–4.52), and increased IgE-associated eczema by 5 years (OR 2.06; 95% CI: 1.02–4.17). A change in 25-OHD levels between birth and 2 years was not associated with allergic outcomes.

CONCLUSIONS. Significantly increased odds of allergic sensitization and/or physician-diagnosed, IgE-mediated allergic disorder or eczema in early childhood were found at the following 25-OHD levels: 21.5 to 29.5 nmol/L from cord blood at birth and 51.7 to 62.6 nmol/L at 2 years of age. 25-OHD levels measured at birth and 2 years of age were nonlinearly associated with allergic sensitization and disease.

REVIEWER COMMENTS. The authors of few studies have evaluated the effect of 25-OHD in early childhood through a prospective study by using measurements of vitamin D at 2 time points. Conflicting results have been published in the literature on the effect of 25-OHD on allergic outcomes. The authors of this study highlight that the relationship between vitamin D and allergy could be nonlinear and warrants further study.

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Vitamin D Supplementation During Pregnancy and Infancy Reduces Aeroallergen Sensitization: A Randomized Controlled Trial

Grant ML, Crane J, Mitchell EA, et al. *Allergy*. 2016;71(9):1325–1334

PURPOSE OF THE STUDY. To determine whether vitamin D supplementation during pregnancy and infancy prevents aeroallergen sensitization and respiratory illness identified by primary care providers.

STUDY POPULATION. Two hundred and sixty women were recruited from an urban primary care maternity clinic in New Zealand from April 2010 to July 2011. The women were managed from 27 weeks' gestation to delivery, and their infants were managed from birth to 18 months of age. Participants were not taking vitamin D supplementation before enrollment.

METHODS. This was a randomized, double-blind, placebo-controlled, parallel-group trial. The mother and infant pairs were randomly assigned to daily placebo and placebo, lower-dose vitamin D (1000 IU/day for mother; 400 IU/day for infant), or higher-dose vitamin D (2000 IU/day; 800 IU/day). When the children were 18 months of age, skin prick testing and specific immunoglobulin E (IgE) antibodies were measured to common aeroallergens including house dust mites (such as *Dermatophagoides farinae* and *Dermatophagoides*

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