



Effect of maternal ω 3 fatty acid supplementation on infant allergy

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The prevalence of atopic disease has steadily increased during the past half century, reaching epidemic proportions in the last several years. The underlying cause is unknown but is likely due to a complex interaction of many factors.^{1–5} The increase seems to follow a geographic pattern of industrialization and is inconsistent with an underlying genetic cause. Because the prevalence of diabetes, cardiovascular disease, and other inflammatory disorders has increased in parallel with that of atopic disease, we hypothesize that nutritional intake is also influencing the development of allergic sensitization.⁶ Because it has drastically changed during the past 20 years, the consumption of dietary fatty acids has been studied as a cause of many of these inflammatory disorders; however, the effect on the development of atopic disease remains unclear.

We aimed to clarify the role of supplementation with the long-chain ω 3 polyunsaturated fatty acids (n-3 PUFAs) docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) during pregnancy on the development of atopic disease, particularly food allergy and eczema. To achieve this aim, a review of the literature was performed that revealed 3 randomized controlled trials that examined the development of food allergy and eczema after n-3 PUFA supplementation during pregnancy. The results of these studies were then applied to the Hennekens criteria, which use chance, bias, confounding, strength of association, biologic plausibility, consistency, temporality, and dose response to attempt to establish causation.

Studies

Study 1 was a randomized controlled trial that examined fish oil supplementation in pregnancy to determine whether it modifies neonatal allergen-specific immune responses and clinical outcomes in infants at high risk of atopy.⁴ This study enrolled 98

pregnant, atopic women from a single hospital in Western Australia. The groups were block randomized according to parity, prepregnancy body mass index, age, and type of maternal allergy. Women in the fish oil group received 3.7 g of an n-3 PUFA that contained 56% DHA (2 g) and 27.7% EPA (1 g). Infants were evaluated for atopic disease at 12 months by history, physical examination, and skin prick testing.

Forty infants from the n-3 PUFA group (35 skin tested) and 43 infants from the control group (37 skin tested) participated in a follow-up appointment at 12 months. No significant difference in diagnosis of eczema was found between the 2 groups (odds ratio [OR], 1.88; 95% confidence interval [CI], 0.77–4.65). Infants from the n-3 PUFA group were 10 times less likely, however, to have severe eczema as measured by the modified SCORAD (Scoring Atopic Dermatitis) index (OR, 0.09; 95% CI, 0.01–0.94).⁷ Infants in the n-3 PUFA group were 3 times less likely to be sensitized to egg at 12 months (OR, 0.34; 95% CI, 0.22–1.02; $P = .06$). No significant difference was found in peanut sensitization between the 2 groups (OR, 0.48; 95% CI, 0.15–2.2; Table 1).

Study 2 examined whether fish oil supplementation in pregnancy and lactation decreases the risk of infant allergy.⁸ One hundred forty-five pregnant women were recruited in 2 Swedish cities for this study. At least one parent or sibling of each unborn child had allergic disease. The groups were block randomized. Women in the n-3 PUFA group received 4.5 mg of fish oil containing 25% DHA (1.6 g) and 35% EPA (1.1 g). Supplementation began at the 25th week of gestation and continued throughout pregnancy and lactation. Infants were evaluated for atopic disease at 3, 6, and 12 months by history, physical examination, and blood allergy testing by ImmunoCap. Skin prick testing was also performed at 6 and 12 months.

Fifty-two dyads were analyzed in the n-3 PUFA group, whereas 65 dyads were analyzed in the placebo group. The period prevalence of eczema at 12 months was 8% in the n-3 PUFA group vs 24% in the control group ($P = .02$). The period prevalence of any positive skin prick test result was 15% in the n-3 PUFA group vs 32% in the placebo group ($P = .04$). Infants in the placebo group were more likely to have a positive skin test result to egg between birth and 12 months (29% vs 12%, $P = .02$). The difference in positive skin prick test results to milk was not significant. Clinical food allergy during the first year of life was also less prevalent in the n-3 PUFA group

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Table 1
ω3 Fatty acid supplementation in pregnancy

Variable	Study		
	Dunstan et al ⁴	Furuhjelm et al ⁸	Palmer et al ⁹
Study design	Randomized controlled trial	Randomized controlled trial	Randomized controlled trial
Study population	98 Pregnant women and mothers with allergic disease from Australia	145 Pregnant women with unborn children with family history of allergic disease from Sweden	706 Pregnant women with unborn children with family history of allergic disease from Australia
Exclusion criteria	Smokers Other medical problems Complicated pregnancies Seafood allergy >2 Meals per week of fish at baseline	Allergy to fish or soy Treatment with anticoagulants Treatment with n-3 PUFAs	Multiple pregnancies Treatment with n-3 PUFAs Known fetal abnormality Bleeding disorder Treatment with anticoagulant Drug or alcohol abuse Participation in another n-3 PUFA trial Non-English speaking Unable to give consent
n-3 PUFA exposure	2 g of DHA 1 g of EPA 20 weeks' gestation through birth	1.6 g of DHA 1.1 g of EPA 25 weeks' gestation through weaning	800 mg of DHA 100 mg of EPA 21 weeks' gestation through birth
Egg sensitization (by skin prick)	OR, 0.34; 95% CI, 0.11–1.02	OR, 0.31; 95% CI, 0.1–0.89 ^a	RR, 0.63; 95% CI, 0.41–0.93 ^a
Peanut sensitization (by skin prick)	OR, 0.22; 95% CI, 0.02–1.8	Not done	RR, 0.63; 95% CI, 0.34–1.2
Clinical food allergy (by skin prick and reaction)	OR, 0.75; 95% CI, 0.2–3.5	OR, 0.09; 95% CI, 0.01–0.7 ^a	RR, 0.96; 95% CI, 0.41–2.3
Eczema (by physician diagnosis)	OR, 1.88; 95% CI, 0.77–4.65	OR, 0.22; 95% CI, 0.06–0.81 ^a	RR, 0.64; 95% CI, 0.40–1.03

Abbreviations: CI, confidence interval; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; n-3 PUFA, ω3 polyunsaturated fatty acid; OR, odds ratio; RR, relative risk.

^a*P* < .05.

compared with controls (4% vs 8%, *P* = .01). The risks of developing any positive skin prick test result (OR, 0.36; 95% CI, 0.14–0.95; *P* < .05), a positive skin prick test result to egg (OR, 0.31; 95% CI, 0.11–0.89; *P* < .05), IgE-associated eczema (OR, 0.22; 95% CI, 0.06–0.81; *P* > .05), and clinical food allergy (OR, 0.09; 95% CI, 0.01–0.74; *P* < .05) were all lower in the n-3 PUFA supplemented group. In addition, an intriguing subanalysis was performed, which found that when the mothers *without* a history of allergic disease were analyzed separately, *no* infants in the n-3 PUFA group developed food allergy, whereas 25% of the placebo group developed food allergy (*P* < .05, Table 1).

Study 3 was a randomized controlled trial that examined the effect of n-3 PUFA supplementation during pregnancy on infants' allergies in the first year of life.⁹ In this trial pregnant women were recruited from 2 hospitals in South Australia and were eligible for the allergy study if the unborn child had a mother, father, or sibling with a history of allergic disease. The groups were block randomized by center and parity. Women in the n-3 PUFA group consumed 1,500 mg of fish oil daily, which contained 800 mg of DHA and 100 mg of EPA. Supplementation began at 21 weeks' gestation and continued until delivery. Allergy follow-up occurred at 1 year of age and included a structured history, clinical examination, and skin prick test.

The 1-year appointment (357 in the n-3 PUFA group and 324 in the control group) was attended by 681 infants, 666 of whom underwent skin prick testing. This study found no difference in the development of clinical food allergy between the n-3 PUFA and control groups (relative risk [RR], 0.96; 95% CI, 0.41–2.25; *P* = .93). Egg sensitization was significantly less in the n-3 PUFA group compared with the control group (RR, 0.62; 95% CI, 0.41–0.93; *P* = .02). Peanut sensitization in both groups was similar, whereas too few infants were sensitized to milk for appropriate analysis. A difference in eczema between the 2 groups was not significant (RR, 0.64; 95% CI, 0.40–1.03; *P* = .06).

Hennekens Criteria

Contrary to previous reviews that were limited by the calculation of a summary OR, these studies offer an intriguing and plausible risk factor for the development of allergic disease in high-risk newborns when applied to the Hennekens criteria (Table 2).^{10,11}

The first 2 studies reviewed suggest that women who supplemented their diet with n-3 PUFAs during pregnancy (and breastfeeding) had 3 times lower odds of their infants developing sensitization to egg in the first year of life and a 5 to 12 times lower odds of eczema. The final study similarly concluded that infants of the women whose diets were supplemented had a significantly lower risk of developing egg allergy in the first year of life and suggested the risk of developing eczema was also reduced. No study was able to conclude that supplementation could reduce the risk of peanut allergy. Intriguingly, Furuhjelm et al⁸ included a subanalysis of mothers *without a history of atopic disease* that demonstrated *no* child developed food allergy in the group who supplemented their diets during pregnancy and breastfeeding compared with 25% of the children in the group who did not supplement their diets, a significant finding. Together, these results, therefore, support a strong association, but not all results are significant and the findings are not consistent across studies.

The plausibility of the association of maternal dietary n-3 PUFAs and food allergy is well supported by previous research. First, the eventual development of allergic disease has been found to be largely predetermined at birth, supporting the role of maternal exposure as a primary influence in their development.¹² Second, the changes in food production has caused a drastic shift in the ratio of n-3 PUFAs to ω6 polyunsaturated fatty acids (n-6 PUFAs) consumed in the average diet of the industrialized world. In 2012, beef, which is now predominantly from corn-fed cows rather than grass-fed cows, is no longer considered an n-3 PUFA-rich food. Although many believe that the ratio of n-6 PUFAs to n-3 PUFAs should not exceed 4, most Americans now consume 20 to 30 times more n-6 PUFAs than n-3 PUFAs.¹³ The n-6 PUFA found in grains, such as corn, elongates to form arachidonic acid, a long-chain n-6 PUFA. Both prostaglandin E₂ and leukotriene B₄, 2 hormones found to drive IgE synthesis, are derived from arachidonic acid. α-Linolenic acid, a short-chain n-3 PUFA fatty acid found in green leaves, is metabolized into EPA and DHA, which counteract the prostaglandin- and leukotriene-driven development of IgE.^{14,15} Finally, fatty acid consumption has been found to significantly influence development of an “anti-inflammatory” intestinal microbiome, a factor that has recently received considerable attention for its potential role in atopic sensitization.¹⁶

Table 2
Assessment of possible causality by the Hennekens criteria

Variable	Study		
	Dunstan et al ⁴	Furuhjelm et al ⁵	Palmer et al ⁹
Chance (95% CI)	Egg (0.11–1.02) Peanut (0.02–1.8) Clinical food allergy (0.1–3.5) Eczema (0.77–4.65) Severe eczema (0.01–0.94)	Egg (0.11–0.89) ^a Peanut (ND) Clinical food allergy (0.01–0.7) ^a Eczema (0.06–0.81) ^a	Egg (0.41–0.93) ^a Peanut (0.34–1.2) Clinical food allergy (0.41–2.3) Eczema (0.40–1.03)
Bias	Insensitive measure bias Observer bias Contamination bias	Insensitive measure bias Observer bias Contamination bias Selection bias	Insensitive measure bias Observer bias Contamination bias
Confounding			
Controlled	Family history Tobacco smoke exposure Birth order Maternal diet: controlled	Family history Timing of food introduction Breastfeeding Tobacco smoke exposure Birth order Maternal diet	Caesarian section Family history Timing of food introduction Breastfeeding Tobacco smoke exposure Birth order Pets Maternal diet
Not controlled	Pets Caesarean section Timing of food introduction Breastfeeding	Caesarean section Pets	
Strength of association	ORs: 0.34 for egg; 0.22 for peanut; 0.75 for clinical food allergy; 1.88 for eczema; 0.09 for severe eczema ^a	ORs: 0.31 for egg ^a ; ND for peanut; 0.09 for clinical food allergy ^a ; and 0.22 for eczema ^a	RRs: 0.63 for egg ^a ; 0.63 for peanut; 0.96 for clinical food allergy; and 0.64 for eczema
Biologic plausibility	Yes, the changes in food production have caused a drastic shift in the ratio of n-3 PUFAs to n-6 PUFAs consumed. Arachidonic acid is an n-6 PUFA that drives IgE synthesis. n-3 PUFAs counteract this synthesis		
Consistency	No, not all studies reached significance but had varying concentrations of n-3 PUFAs administered		
Temporality	Yes, exposure occurs during susceptible period of fetal development		
Dose response	Possible, the study by Furuhjelm et al had the highest exposure and most protection against clinical food allergy and egg sensitization		

Abbreviations: CI, confidence interval; n-3 PUFA, ω 3 polyunsaturated fatty acid; n-6 PUFA, ω 6 polyunsaturated fatty acid; ND, not determined; OR, odds ratio; RR, relative risk.

^a $P < .05$.

A possible dose response can be seen across these studies because the study with the most accentuated results is also the study with the highest cumulative dose of EPA and DHA given. Although the first study does not report the length of supplementation, the dose of EPA and DHA given was high but not continued through breastfeeding. Further, the second study that resulted in the most pronounced protective effect provided approximately 5 times the overall dose of DHA and 30 times the overall dose of EPA as the third study, in which the only significant finding was a decrease in egg sensitization. This observation supports causality.

These studies have several limitations that must be considered when interpreting the results. A primary concern in all 3 studies is a contamination bias in the placebo groups through dietary n-3 PUFA consumption. The first 2 trials attempted to control for this by administration of food frequency questionnaires and 24-hour food diaries. Both of these methods, however, have received substantial criticism for the inaccuracy of their results.¹⁷ All 3 studies compared maternal phospholipids at childbirth, which offers reassurance because the treatment group had significantly higher levels of blood n-3 PUFAs. Observer bias is also a concern because several patients in these trials who supplemented their diet with n-3 PUFAs reported “burping” a fish taste, which would have effectively unblinded them and potentially influenced the diagnosis of eczema and the skin test results. Randomization was also not well described in the study by Furuhjelm et al, the study with the most striking results, where, despite randomization, arachidonic acid levels before intervention were lower in the placebo group. However, because the placebo group was the group with lower arachidonic acid levels, equal arachidonic acid levels at randomization would likely have led to even lower ORs. Finally, because allergic sensitization does not equate to clinical food allergy, the overall relevance of sensitization can be questioned.

These studies provide compelling but insufficient evidence to conclude that maternal fatty acid consumption influences infant food allergy. If high-dose n-3 PUFA supplementation has an immunomodulatory effect, the required dose is likely greater than doses previously studied to enhance developmental outcomes and, if limited to use during pregnancy, greater than doses that are commercially available today. Overall, a positive effect would have a striking public health implication because the study by Furuhjelm et al, with the highest level and longest duration of supplementation, found a number needed to treat of only 6 to prevent eczema and 7 to prevent infant food allergy, a potentially lifelong condition. Dietary supplementation of mothers with high-risk infants is therefore likely to be cost-effective, particularly considering the associated cognitive and cardiac benefits of n-3 PUFAs.^{18,19} Future research is needed, however, to further clarify several questions before large-scale implementation of this preventive strategy, namely (1) to determine whether high-dose n-3 PUFA supplementation from conception (or preconception) through breastfeeding further augments this protective effect, (2) to demonstrate the effect in the diverse American population, (3) to demonstrate the long-term effect on the development of asthma and allergic rhinitis, and (4) to demonstrate whether a diet high in green leafy vegetables, fish, and grass-fed beef alone can alter the current course of the atopic epidemic.

References

- [1] Priftis KN, Mantzouranis EC, Anthracopoulos MB. Asthma symptoms and airway narrowing in children growing up in an urban versus rural environment. *J Asthma*. 2009;46:244–251.
- [2] Kang BC, Johnson J, Veres-Thorner C. Atopic profile of inner-city asthma with a comparative analysis on the cockroach-sensitive and ragweed-sensitive subgroups. *J Allergy Clin Immunol*. 1993;92:802–811.
- [3] Martino D, Prescott S. Epigenetics and prenatal influences on asthma and allergic airways disease. *Chest*. 2011;139:640–647.
- [4] Dunstan JA, Mori TA, Barden A, et al. Fish oil supplementation in pregnancy modifies neonatal allergen-specific immune responses and clinical outcomes

- in infants at high risk of atopy: a randomized, controlled trial. *J Allergy Clin Immunol*. 2003;112:1178–1184.
- [5] Martinez FD, Cline M, Burrows B. Increased incidence of asthma in children of smoking mothers. *Pediatrics*. 1992;89:21–26.
- [6] Watson PE, McDonald BW. Subcutaneous body fat in pregnant New Zealand women: association with wheeze in their infants at 18 months. *Matern Child Health J*. 2013;17:959–967.
- [7] Angelova-Fischer I, Bauer A, Hipler UC, et al. The objective severity assessment of atopic dermatitis (OSAAD) score: validity, reliability and sensitivity in adult patients with atopic dermatitis. *Br J Dermatol*. 2005;153:767–773.
- [8] Furuholm C, Warstedt K, Larsson J, et al. Fish oil supplementation in pregnancy and lactation may decrease the risk of infant allergy. *Acta Paediatr*. 2009;98:1461–1467.
- [9] Palmer DJ, Sullivan T, Gold MS, et al. Effect of n-3 long chain polyunsaturated fatty acid supplementation in pregnancy on infants' allergies in first year of life: randomised controlled trial. *BMJ*. 2012;344:e184.
- [10] Klemens C, Berman D, Mozurkewich E. The effect of perinatal omega-3 fatty acid supplementation on inflammatory markers and allergic diseases: a systematic review. *BJOG*. 2011;118:916–925.
- [11] Anandan C, Nurmatov U, Sheikh A. Omega 3 and 6 oils for primary prevention of allergic disease: systematic review and meta-analysis. *Allergy*. 2009;64:840–848.
- [12] Prescott SL, Macaubas C, Holt BJ, et al. Transplacental priming of the human immune system to environmental allergens: universal skewing of initial T cell responses toward the Th2 cytokine profile. *J Immunol*. 1998;160:4730–4737.
- [13] Simopoulos AP. Essential fatty acids in health and chronic disease. *Am J Clin Nutr*. 1999;70(3 suppl):560S–569S.
- [14] Ohmori H, Hikida M, Takai T. Prostaglandin E2 as a selective stimulator of antigen-specific IgE response in murine lymphocytes. *Eur J Immunol*. 1990;20:2499–2503.
- [15] Miyahara N, Takeda K, Miyahara S, et al. Requirement for leukotriene B4 receptor 1 in allergen-induced airway hyperresponsiveness. *Am J Respir Crit Care Med*. 2005;172:161–167.
- [16] Caicedo RA, Schanler RJ, Li N, Neu J. The developing intestinal ecosystem: implications for the neonate. *Pediatr Res*. 2005;58:625–628.
- [17] Byers T. Food frequency dietary assessment: how bad is good enough? *Am J Epidemiol*. 2001;154:1087–1088.
- [18] Greenberg J, Bell SJ, Ausdal WV. Omega-3 fatty acid supplementation during pregnancy. *Rev Obstet Gynecol*. 2008;1:162–169.
- [19] Kris-Etherton PM, Harris WS, Appel LJ. Fish consumption, fish oil, omega-3 fatty acids, and cardiovascular disease. *Circulation*. 2002;106:2747–2757.