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The Effect of Maternal Omega-3 Fatty Acid Supplementation on Infant Allergy

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Introduction

The prevalence of atopic disease has steadily increased over the past half century, reaching epidemic proportions in the last several years. The underlying cause is unknown but likely due to a complex interaction of many factors.[1–5] The increase does seem to follow a geographic pattern of industrialization and is inconsistent with an underlying genetic cause. As the prevalence of diabetes, cardiovascular disease and other inflammatory disorders have increased in parallel with that of atopic disease, we hypothesize that nutritional intake is also influencing the development of allergic sensitization.[6] As it has drastically changed over 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 the long chain omega-3 polyunsaturated fatty acids, (n-3 PUFA) docosahexaenoic acid (DHA) and eicosapentaenoic acid, (EPA) supplementation during pregnancy on the development of atopic disease, particularly food allergy and eczema. In order to achieve this aim, a review of the literature was performed that revealed three randomized controlled trials which examined the development of food allergy and eczema after n-3 PUFA supplementation during pregnancy. The results of these studies were then applied to Hennekens' criteria, which uses chance, bias, confounding, strength of association, biologic plausibility, consistency, temporality, and dose-response to attempt to establish causation.

Studies

Study 1: 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[4]

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

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Forty infants participated in a follow-up appointment at 12 months from the n-3 PUFA group (35 skin tested) and 43 infants participated from the control group (37 skin tested). No significant difference in diagnosis of eczema was found between the two groups (OR 1.88; 95% 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 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=0.055). No significant difference was found in peanut sensitization between the two groups (OR 0.48; 95% CI 0.15–2.2, Table 1).

Study 2: Fish oil supplementation in pregnancy and lactation may decrease the risk of infant allergy.[8]

One hundred forty-five pregnant women were recruited in two 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 grams) and 35% EPA (1.1 grams). Supplementation began at the 25th week gestation and continued throughout pregnancy and lactation. Infants were evaluated for atopic disease at 3, 6, and 12 months by history, examination and blood allergy testing by Immunocap. Skin prick test was also completed at 6 and 12 months.

Fifty-two dyads were analyzed in the n-3 PUFA group; while 65 dyads were analyzed in the placebo group. The period prevalence of eczema at 12 months was 8% in the n-3 PUFA group versus 24% in the control group (p=0.02). The period prevalence of any positive skin prick test was 15% in the n-3 PUFA group versus 32% in the placebo group (p=0.04). Infants in the placebo group were more likely to have a positive skin test to egg between birth and 12 months (29% versus 12% respectively, p=0.02). The difference in positive skin prick tests to milk was not significant. Clinical food allergy during the first year of life was also less prevalent in the n-3 PUFA group as compared to controls (4% versus 8% respectively, p=0.01). The risk of developing any positive skin prick test (OR 0.36; 95% CI 0.14,0.95; p<0.05), a positive skin prick to egg (OR 0.31; 95% CI 0.11,0.89; p<0.05), IgE associated eczema (OR 0.22; 95% CI 0.06,0.81; p>0.05) and clinical food allergy (OR 0.09; 95% CI 0.01,0.74; p<0.05) 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; while, 25% of the placebo group developed food allergy (p<0.05, Table 1).

Study 3: Effect of n-3 long chain polyunsaturated fatty acid supplementation in pregnancy on infants' allergies in first year of life: randomised controlled trial[9]

In this trial pregnant women were recruited from two hospitals in South Australia and eligible for the allergy study if the unborn baby 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 1500mg of fish oil daily which contained 800mg DHA and 100mg 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 n-3 PUFA; 324 control) was attended by 681 infant and 666 infants had skin prick tests. This study found no difference in the development of clinical food allergy between the n-3 PUFA and control groups (RR=0.96; 95% CI 0.41,2.25; p=0.93). Egg sensitization was significantly less in the n-3 PUFA group as compared to the control group (RR=0.62; 95% CI 0.41,0.93; p=0.02). Peanut sensitization in both groups was similar; while, too few infants were sensitized to milk for appropriate analysis. A

difference in eczema between the two groups approached significance (RR 0.64, 95% CI 0.40,1.03, p=0.06).

Hennekens' Criteria

Contrary to previous reviews that were limited the calculation of a summary odds ratio, these studies offer an intriguing and plausible risk factor for the development of allergic disease in high risk newborns when applied to Hennekens' Criteria (Table 2).[10,11] The first two studies reviewed suggest that women who supplemented their diet with n-3 PUFA during pregnancy (and breastfeeding) had three times lower odds of their infants developing sensitization to egg in the first year of life and a five to twelve 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 al 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 as compared to 25% of the children in the group that did not supplement their diets, a significant finding. These results together, 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 PUFA and food allergy is well supported by previous research. First, the eventual development of allergic disease has been shown to be largely predetermined at birth supporting the role of maternal exposure as a primary influence in their development.[2] Second, the changes in food production has caused a drastic shift in the ratio of n-3 PUFA to omega-6 polyunsaturated fatty acids (n-6 PUFA) 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 omega-3 rich food. Although many believe that that ratio of n-6 PUFA:n-3 PUFA should not exceed 4, most American's now consume 20–30 times more n-6 PUFA then n-3 PUFA.[3] 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, two hormones shown to drive IgE synthesis, are derived from arachidonic acid. α-Linolenic acid, a short chain omega-3 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 shown to significantly influence development of an "anti-inflammatory" intestinal microbiome, a factor which has recently received considerable attention for its potential role in atopic sensitization.[16]

A possible dose-response can be seen across these studies, as 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 which resulted in the most pronounced protective effect provided approximately five 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 three studies is a contamination bias in the placebo groups through dietary n-3 PUFA consumption. The first two 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 three studies compared maternal phospholipids at childbirth which does offer reassurance as the treatment group did have significantly higher levels of blood n-3 PUFA. Observer bias is also a concern as several patients in these trials who supplemented their diet with n-3 PUFA reported “burping” a fish taste which would have effectively unblinded them and potentially influenced the diagnosis of eczema as well as 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 prior to intervention were lower in the placebo group. However, as the placebo group was the group with lower arachidonic acid levels, equal arachidonic acid levels at randomization would likely have led to even lower odds ratios. Finally, as allergic sensitization does not equate to clinical food allergy and the overall relevance of sensitization can be questioned.

Conclusions

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 does have 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 as the Furuhjelm study, 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 life-long 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 PUFA.[18, 19] Future research is needed, however, to further clarify several questions prior to large scale implementation of this preventive strategy, namely 1) to determine if 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.

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Table 1

Omega-3 fatty acid supplementation in pregnancy

	Study #1	**Study #2**	**Study #3**
Citation	Dunstan et al. JACI	Furuhjelm et al. Acta Paediatrica	Palmer et al. BMJ
	2003; 112:1178–84	2009;98:1461–7	2012;344:e184
Study Design	Randomized Control Trial	Randomized Control Trial	Randomized Control Trial
Study Population	98 pregnant women	145 pregnant women	706 pregnant women
	Mother with allergic disease	Unborn child with FH of allergic disease	Unborn child with FH of allergic disease
	Australia	Sweden	Australia
	Exclusion Criteria:	Exclusion Criteria:	Exclusion Criteria:
	Smokers	Allergy to fish or soy	Multiple pregnancy
	Other medical problems	Treatment with anticoagulants	Treatment with n-3 PUFA
	Complicated pregnancies	Treatment with n-3 PUFA	Known fetal abnormality
	Seafood allergy		Bleeding disorder
	>2 meals/wk of fish at baseline		Treatment with anticoagulant
			Drug/alcohol abuse
			Participation in another n-3 PUFA trial
			Non-English speaking
			Unable to give consent
n-3 PUFA Exposure	2g DHA	1.6g DHA	800mg DHA
	1g EPA	1.1g EPA	100mg EPA
	?? weeks gestation through birth	25 weeks gestation through wean	21 weeks gestation through birth
Egg Sensitization (by skin prick)	OR 0.34	** OR 0.31	** RR 0.63
	95% CI (0.11, 1.02)	95% CI (0.1, 0.89)	95% CI (0.41, 0.93)
Peanut Sensitization (by skin prick)	OR 0.22	Not Done	RR 0.63
	95% CI (0.02, 1.8)		95% CI (0.34, 1.2)
Clinical Food Allergy (by skin prick and reaction)	OR 0.75	** OR 0.09	RR 0.96
	95% CI (0.2, 3.5)	95% CI (0.01, 0.7)	95% CI (0.41, 2.3)
Eczema (by physician diagnosis)	OR 1.88	** OR 0.22	RR 0.64
	95% CI (0.77,4.65)	95% CI (0.06,0.81)	95% CI (0.40,1.03)

Abbreviations: BMJ, British Medical Journal; CI, confidence interval; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; FH, family history; JACI, Journal of Allergy and Clinical Immunology; n-3 PUFA, omega-3 polyunsaturated fatty acid; OR, odds ratio; wk, week

** $p<0.05$

Table 2

Assessment of Possible Causality by Hennekens' Criteria

	Study #1	Study #2	Study #3
Chance (95% CI)	Egg (0.11, 1.02)	** Egg (0.11, 0.89)	** Egg (0.41, 0.93)
	Peanut (0.02, 1.8)	Peanut (ND)	Peanut (0.34, 1.2)
	Clinical food allergy (0.1, 3.5)	** Clinical food allergy (0.01, 0.7)	Clinical food allergy (0.41, 2.3)
	Eczema (0.77,4.65)	** Eczema (0.06, 0.81)	Eczema (0.40, 1.03)
	Severe eczema (0.01,0.94)		
Bias	Insensitive Measure Bias	Insensitive Measure Bias	Insensitive Measure Bias
	Observer Bias	Observer Bias	Observer Bias
	Contamination Bias	Contamination Bias	Contamination Bias
		Selection Bias	
Confounding	Controlled:	Controlled:	Controlled:
	Family History	Family History	C-Section
	Tobacco Smoke exposure	Timing of food intro	Family History
	Birth order	Breastfeeding	Timing of food intro
	Maternal diet: controlled	Tobacco Smoke exposure	Breastfeeding
		Birth order	Tobacco smoke exposure
	Not controlled	Maternal diet	Birth order
	Pets		Pets
	C-section	Not controlled:	
	Timing of food intro	C-section	Not controlled:
	Breastfeeding	Pets	Maternal diet
Strength of Association	OR (egg): 0.34	** OR (egg): 0.31	** RR (egg): 0.63
	OR (peanut): 0.22	OR (peanut): ND	RR (peanut): 0.63
	OR (clinical food allergy): 0.75	** OR (clinical food allergy): 0.09	RR (clinical food allergy): 0.96
	OR (eczema): 1.88	** OR (eczema): 0.22	RR (eczema): 0.64
	** OR (severe eczema): 0.09		
Biologic	Yes, the changes in food production has caused a drastic shift in n-3 PUFA:n-6 PUFA consumed.		
Plausibility	Arachidonic acid is an n-6 PUFA that drives IgE synthesis. n-3 PUFA counteract this synthesis.		
Consistency	No, not all studies reached significance but had varying concentrations of n-3 PUFA administered		
Temporality	Yes, exposure occurs during susceptible period of fetal development.		
Dose-Response	Possible, study #2 with highest exposure and most protection against clinical food allergy and egg sensitization		

Abbreviations: CI, confidence interval; n-3 PUFA, omega-3 polyunsaturated fatty acid; n-6 PUFA; omega-6 polyunsaturated fatty acid; OR, odds ratio; RR, relative risk

** $p<0.05$