

Prevention of Asthma: Fish or Fish Oil?

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Practice Options from Beyond Our Pages focuses on identifying, critiquing, and placing into context research studies published in other journals that have the potential to change our clinical practices. It is written by Allergy-Immunology Fellows partnered with faculty members, and does not require an invitation for submission. This feature is coordinated by Editorial Board members Matthew Rank, MD and Julie Wang, MD.

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BACKGROUND

Although asthma control can be achieved in most subjects, there is no known cure. Primary prevention of any disease, including asthma, is ideal. Probiotics, antihistamines, inhaled glucocorticosteroids, allergen and/or irritant avoidance, allergen immunotherapy, and even biologics have been investigated to prevent its onset, with mixed results.¹ However, fish oil, enriched in n-3 polyunsaturated fatty acids (PUFA), for example, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), used during pregnancy, may prevent asthma in progeny. The proposed mechanism is that EPA and DHA replace arachidonic acid on cell membranes and result in a reduction of arachidonic acid transformation into proinflammatory leukotrienes, known to cause airway inflammation and bronchoconstriction.² A 2015 Cochrane review demonstrated limited evidence to support fish oil supplementation during pregnancy to reduce asthma onset in offspring, although the conclusion was based on few studies with various supplementation dosages, research quality, and statistical power.³ However, 2 publications, one by Bisgaard et al⁴ (study A) and another by Hansen et al⁵ (study B), published in 2016 and 2017, respectively, in which high-dose fish oil

supplementation was used during the third trimester, were successful to prevent pediatric asthma.

METHODS

Study A

Pregnant women at 24 weeks of gestation were double-blind, placebo-controlled, randomized to receive 2.4 g of n-3 PUFA (N = 346) or placebo olive oil (N = 349) daily until 1 week after delivery in the years 2008 to 2010. The amount of 2.4 g of n-3 PUFA contains 1320 mg of EPA and 888 mg of DHA. The primary end point was persistent wheeze or asthma diagnosis in offspring when followed prospectively over 5 years. Both investigators and subjects remained blinded until the youngest child in the study reached 3 years of age. Maternal serum EPA and DHA levels were obtained at the time of randomization and 1 week after delivery.⁴

Study B

Pregnant women at 30 weeks of gestation were randomized to receive 2.7 g of n-3 PUFA (N = 266), olive oil (N = 136), and no oil group (N = 131). The fish oil and olive oil groups consisted of a double-blinded individual daily supplementation and remained blinded until delivery. The amount of 2.7 g of n-3 PUFA contains 1280 mg of EPA and 920 mg of DHA. The no oil group was informed of the trial proposal and the advantage of fish oil, and was considered as a passive intervention control group. All offspring were followed for up to 24 years of age. The primary outcome was the prescription rate of related asthma and allergic rhinitis medications.⁵

RESULTS

Study A

The risk of persistent wheezing or asthma in the progeny at 5 years of age was 16.9% in the fish oil versus 23.7% in the olive oil group, a relative reduction (RR) of 30.7% ($P = .035$). The strongest effect in a subgroup analysis occurred in the lowest third of the maternal serum EPA and DHA group with an RR of 54.1% ($P = .011$). The other two-third of moderate and high baseline EPA and DHA trial population was not statistically significant in risk reduction. There were no statistically significant changes in asthma exacerbation, eczema, allergic rhinoconjunctivitis, lung function, or allergen sensitization except for a reduction in lower respiratory tract infections in the fish oil group in the secondary end point analyses.

Study B

The hazard ratio (HR) of related prescribed asthma medications in the progeny at 24 years of age was 0.54 in the fish oil

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compared with the olive oil group ($P = .02$). The HR of related prescribed allergic rhinitis medications in the fish oil compared with the olive oil group was 0.7, not statistically significant ($P = .09$). However, the “no oil” versus the fish oil group had the highest HR reduction in contrast with the fish oil group (0.43 vs 0.54) in related asthma medications and (0.66 vs 0.7) in related allergic rhinitis medications as illustrated in Table I. There were no statistically significant differences among all groups for lung function outcomes, biomarkers, and allergen sensitization at age 18 to 19 years.

CRITICAL APPRAISAL

These 2 studies evaluate the therapeutic effect of fish oil in asthma prevention. There is no confounding by maternal history of asthma that could affect both study outcomes.^{5,6} Both conclude that high-dose (2.4-2.7 g of n-3 PUFA) fish oil supplementation, primarily during the third trimester, may prevent the onset of asthma from early infancy through adolescence. The approximate daily dose, which requires 7 to 8 commercial fish oil softgels a day, and monthly cost for commercial fish oil are calculated in Table II.

As demonstrated in study A, only the offspring of pregnant women with the lowest third EPA and DHA levels benefited from fish oil supplementation. However, this finding generates several questions that include the following: (1) Should physicians screen for EPA and/or DHA levels during pregnancy? (2) At what exact EPA and/or DHA levels should physicians intervene? and (3) How often should EPA and/or DHA levels be determined?

Rather than instituting this complicated scenario, a better alternative way may be to recommend consuming fish during pregnancy. Because EPA and DHA are almost exclusively from fish and shellfish, it is reasonable to hypothesize that enough fish consumption could provide the same benefit as fish oil. An earlier study demonstrates that the progeny of pregnant women with no fish ingestion are at higher risk to develop asthma and asthma-related admissions and prescriptions when compared with pregnant women consuming fish as in a sandwich or hot meal ≥ 2 to 3 times per week.⁷ Furthermore, postpartum questionnaires from study B indicate an increased frequency in fish intake and self-supplementation in the “no oil” group compared with the olive oil group. This reinforces the proposition that passive ingestion of fish may have the same benefit as fish oil supplementation.⁵

The Food and Drug Administration (FDA) and Environmental Protection Agency (EnPA) finalized their recommendation regarding fish consumption in January 2017.⁸ The FDA previously published data indicate that more than 50% of pregnant women eat less than 2 ounces of fish per week.⁹ Both organizations joined force to recommend that 8 to 12 ounces of low-mercury fish per week be consumed during pregnancy, equal to 2 to 3 fish servings per week, because of the nutritional benefit for infant growth and development.¹⁰ The minimum of 8 ounces of fish intake per week, as recommended by the FDA/EnPA, is more than the calculated median fish intake (6.42 ounces/week) in the moderate serum EPA and DHA level group from study A, which did not attain benefit from fish oil supplementation in asthma prevention.

Of possible concern is the amount of mercury contained in fish. The mercury level from ingesting marine animals is compared with the reference dose defined by the exposure rate

TABLE I. Adapted primary outcomes from study B⁵

Registry-based outcomes	Hazard ratio (95% confidence interval)
Asthma medication	
Fish oil	0.54 (0.32-0.90)
No oil	0.43 (0.22-0.85)
Olive oil	1.00
	$P = .02$
Allergic rhinitis medication	
Fish oil	0.70 (0.47-1.05)
No oil	0.66 (0.40-1.08)
Olive oil	1.00
	$P = .09$

TABLE II. Calculation examples of daily dosage and monthly cost of commercial fish oil and fish (sample price from local pharmacy and market in Tampa, Fla)

Fish oil	Commercial fish oil	Study by Bisgaard et al ⁴	Study by Hansen et al ⁵
Ingredients	One softgel of 360 mg n-3 PUFA contains EPA 180 mg and DHA 120 mg 0.1 dollars/softgel	Daily dosage of 2400 mg n-3 PUFA contains EPA 1320 mg and DHA 888 mg	Daily dosage of 2700 mg n-3 PUFA contains EPA 1280 mg and DHA 920 mg
Approximate dose per day using commercial fish oil		1320/180 = 7.3 888/120 = 7.4 7-8 softgels/d	1280/180 = 7.1 920/120 = 7.6 7-8 softgels/d
Monthly cost		21-24 dollars/mo	
Fish		Farmed salmon, fresh	
Market price		11.99 dollars/pound	
8-12 ounces of fish per week		6-9 dollars/wk	
Monthly cost		24-36 dollars/mo	

DHA, Docosahexaenoic acid; EPA, eicosapentaenoic acid; PUFA, polyunsaturated fatty acids.

that one individual will experience over a lifetime without the appreciable risk of harm in the FDA/EnPA report.¹¹ The highest allowable average mercury concentration in fish, when consuming 3 servings per week, is 0.15 $\mu\text{g/g}$. In short, 8 to 12 ounces per week of fish, with an average mercury concentration less than or equal to 0.15 $\mu\text{g/g}$, can be safely consumed.¹¹ Four species of fish with high mercury levels that should be avoided include tilefish from the Gulf of Mexico and shark, swordfish, and king mackerel from throughout the world. Most other fish contain considerably less mercury. Fish species with mercury levels below or equal to 0.15 $\mu\text{g/g}$ are listed in Table III. These fish contain high to low combined EPA and DHA levels. In contrast to fish, commercial fish oil supplements contain undetectable to trace amount ($<0.01 \mu\text{g/g}$) of mercury.

TABLE III. Recommendation fish list for average fish mercury concentration ≤ 0.15 $\mu\text{g/g}$ with the corresponding high to low EPA plus DHA level, adapted from FDA and EnPA joint advice¹⁰

Fish species	Mercury concentration average, $\mu\text{g/g}$ (95% confidence interval)	EPA plus DHA (g/100 g fish)
Anchovy	0.02 (0.01-0.02)	2.02
Shad	0.04 (0.02-0.06)	2.02
Herring	0.08 (0.04-0.13)	2.02
Pacific chub mackerel	0.09 (not calculated)	1.25
Atlantic mackerel	0.05 (not calculated)	1.20
Sardine	0.01 (0.01-0.02)	1.19
Salmon, canned	0.01 (0.005-0.02)	1.18
Salmon, fresh/frozen	0.02 (0.02-0.03)	1.18
Black sea bass	0.13 (0.10-0.16)	0.97
Trout, freshwater	0.07 (0.03-0.12)	0.93
Whitefish	0.09 (0.06-0.12)	0.91
Smelt	0.08 (0.05-0.13)	0.89
Butterfish	0.06 (not calculated)	0.73
Pollock	0.03 (0.02-0.05)	0.53
Mullet	0.05 (0.02-0.09)	0.32
Perch, ocean	0.12 (0.08-0.17)	0.32
Flatfish	0.06 (0.04-0.07)	0.30
Skate	0.14 (not calculated)	0.30
Perch, freshwater	0.15 (0.10-0.20)	0.29
Tuna, light, canned	0.13 (0.12-0.14)	0.27
Catfish	0.02 (0.01-0.04)	0.22
Atlantic croaker	0.07 (0.06-0.08)	0.20
Haddock	0.06 (0.05-0.06)	0.16
Hake	0.08 (0.06-0.10)	0.16
Cod	0.11 (0.09-0.14)	0.16
Tilapia	0.01 (0.01-0.02)	0.09

DHA, Docosahexaenoic acid; EnPA, Environmental Protection Agency; EPA, eicosapentaenoic acid; FDA, Food and Drug Administration.

n-3 PUFA cannot be synthesized by humans and therefore are essential nutrients. Both fish oil and fish contain these fatty acids. The 2 above-mentioned studies demonstrate that high-dose fish oil supplementation during the third trimester of pregnancy can reduce the risk of developing childhood asthma. However, the ingestion of appropriate low-mercury-containing fish seems to be a better approach than does the use of fish oil supplementation. Fish also contain other desired nutrients including high-quality proteins, minerals, and vitamins. The price of fish oil supplementation or different fish species varies geographically, and individual economic status should also be taken into account (Table II). Ideally, a

head-to-head cohort study that randomizes low serum EPA and DHA level pregnant women into a “fish oil” versus a “fish” group would determine if high fish oil supplementation or increased fish intake alone is equally beneficial or if one is more beneficial than the other.

RECOMMENDATION

It is premature to recommend high-dose n-3 PUFA (2.4-2.7 g) fish oil supplementation during the third trimester to prevent pediatric asthma due to unclear screening, threshold level, and testing interval. However, low-mercury fish intake of 8 to 12 ounces per week for pregnant women from FDA/EnPA recommendation may reduce the risk of developing childhood asthma. Physicians should provide the best practical recommendation based on the evidence, benefits/risks, and cost.

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