

Omega-3 fatty acids and asthma in children

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ABSTRACT

The purpose of this study was to summarize and analyze the results of studies supporting the use of omega-3 fatty acids for their therapeutic and preventive value in childhood asthma in light of recent genetic evidence strongly suggesting a pathogenetic role in asthma and to discuss the implications of these findings for future research. Although a considerable number of observational studies have been conducted in children showing a beneficial effect of omega-3 dietary intake in asthma, a fully well-designed, rigorously conducted investigational study is still lacking. Additionally, the few interventional trials with omega-3 supplementation conducted in asthmatic children have often yielded conflicting results. The genetic polymorphism and the gene–nutritional interactions that accompany asthma can be the missing factors and may explain the inconsistent results found in these interventional trials. Therefore, the analyses of key genes variants should be included in future studies to thoroughly investigate the effects of long-chain polyunsaturated fatty acid on asthma. Although a definitive conclusion can not be made supporting a beneficial effect of dietary modification or supplementation with omega-3 for the prevention or modification of asthmatic disease in children, there is sufficient evidence to support this possibility. There is, therefore, a clear need for future research to investigate the feasibility of this dietetic approach to reduce the likely development of asthma and/or the successful treatment of asthmatic disease. From a public health perspective, if a dietetic approach is successfully documented, even if only in a cohort of susceptible individuals, it would offer a far better management tool than currently available, better tolerated, and, in the long run, more cost-effective.

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Over the past few decades, a dramatic increase in the prevalence of allergic diseases and asthma has been seen with the highest incidence occurring in children.¹ This phenomenon has occurred so rapidly that it has been hypothesized to be related to environmental changes, rather than genetic predisposition, a phenomenon heavily published in the literature as the “hygiene hypothesis.”² This hypothesis proposes that western lifestyle limits general microbial exposure and alters the colonization of the infant gut inducing allergic disease later in childhood. The most accredited immunologic explanation underpinning the hygiene hypothesis is that some bacterial infections during early life lead to an increase in anti-inflammatory cytokines, such as IL-10, that down-regulate Th2 responses, causing a decrease in allergic diseases.³

Probiotics have been shown to normalize intestinal permeability and balance gut microecology, improve the intestine’s immunologic defense barrier (e.g., IgA), alleviate intestinal inflammatory responses, and down-

regulate proinflammatory cytokines characteristic of local and systemic allergic inflammation.^{4–9}

Lactobacillus rhamnosus GG probiotic seems to be a useful adjunct therapy for food hypersensitivity by decreasing intestinal inflammation in atopic children with a history of cow’s milk allergy.¹⁰ Fifty percent of skin test–positive patients with milk antigen had decreased IL-4 ($p = 0.06$) and TNF- α ($p < 0.05$) by *L. rhamnosus* GG probiotic treatment. In skin test–negative atopic dermatitis patients, no change or increased levels were noted with or without probiotic.¹¹

In contrast, obesity¹² and changes in the diet of western countries, especially in its fatty acid composition, have been suggested to be partly responsible for this epidemiological trend. The retrospective study of Malik *et al.*¹³ indicated that obesity is associated with asthma with a number of possible mechanisms mentioning that adipose tissue explants secrete eotaxin and diet-induced weight loss can lead to reduction in plasma eotaxin levels and that clinical interventions that target obesity can modulate these levels. Moreover, atopic asthmatic subjects had significantly higher leptin levels than did nonatopic subjects.^{14,15} Regarding the changes in the diet, dietary intake of animal fat has progressively decreased, whereas the consumption of margarine and vegetable oils containing *n*-6 polyunsaturated fatty acids (PUFA) has increased in western diets as a consequence of public health measures to reduce coronary heart disease.¹⁶ These dietary changes, in turn,

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have led to a progressive imbalance of the omega-6 to omega-3 PUFA ratio that has risen considerably from a range of 1:1–2:1 to 20:1–30:1 in recent years.¹⁷ In 1997 Black and Sharpe hypothesized that atopic sensitization and inflammation could be promoted by a change in dietary intake of PUFAs. They argued that the increase of linolenic acid (LA) dietary intake resulted in raised arachidonic acid (AA) and prostaglandin E₂ production, with a consequent increase in atopic Th2 sensitization, asthma, and atopic disease.¹⁸

The Black and Sharpe hypothesis is historically important because it represented the starting point for intervention trials of dietary supplementation with omega-3 in asthma. Overall, the results of these trials performed mostly in adults, however, were disappointing, showing no consistent effects on either clinical or functional respiratory parameters.^{19,20} The few intervention trials performed in children yielded conflicting results.^{21–23}

This article summarizes the evidence about the effects of omega-3 consumption and supplementation on asthma in children, proposing new possible explanations for the discordant results of some clinical studies, also in light of the most recent findings in terms of genetics, and discusses the implications for the future research. Before presenting this information, a brief description of long-chain PUFA (LCPUFA) omega-3 and omega-6 metabolism is presented.

LCPUFAS: STRUCTURE, SOURCES, METABOLIC PATHWAYS, AND RECENT INSIGHTS IN THE INFLAMMATORY PROCESSES

LA (C18:2n-6), a precursor to the *n*-6 series of fatty acids, and alfa-LA (C18:3n-3), a precursor to the *n*-3 series of fatty acids, are the simplest members of each family of PUFA. They are termed essential because they can not be synthesized by the organism, so they must be obtained from the diet.

Although mammalian cells can not synthesize LA and alfa-LA, they can metabolize them into more physiologically active compounds by the introduction of additional double bonds (desaturation) *via* δ -5 desaturase and δ -6 desaturase that are encoded by FADS1 and FADS2 genes, respectively, and by lengthening the acyl chain *via* elongases. The major end product of the *n*-6 pathway is AA, whereas the major end products of the *n*-3 pathways are eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA).

Four-series leukotrienes and the two-series prostaglandins are characterized by a strong proinflammatory action.^{24,25} The two-series prostaglandins exert effects also on immune cells. They are known to have immunomodulatory properties, promoting the Th2 phenotype associated with asthma and atopic disease.²⁶ Recent studies have identified a novel group of

potent mediators, termed E- and D-series resolvins, formed from EPA and DHA, respectively. Resolvins are local-acting mediators possessing potent anti-inflammatory and immunoregulatory properties.^{27,28}

Another key anti-inflammatory effect of *n*-3 PUFAs is mediated at the level of altered inflammatory gene expression through modifications of transcription factor activity such as nuclear factor κ B (NF- κ B) and peroxisome proliferator-activated receptors.²⁹ NF- κ B is a transcription factor that plays an important role in various inflammatory signaling pathways.³⁰ NF- κ B pathway is an important transcription factor in immune system responses, essential for reprogramming the expression of genes that control B-cell survival and proliferation. The activated NF- κ B leads to the up-regulation of proinflammatory genes and production of cytokines, which leads to greater inflammation.³¹ Supplementing pregnant women with fish oil can induce immunologic changes in cord blood and in some studies decreases sensitization to common food allergens to lower the prevalence and severity of atopic dermatitis in the 1st year of life and the protective effect of maternal *n*-3 PUFAs may last until adolescence of the offspring.²¹

CLINICAL STUDIES

For ease of discussion, the clinical studies considered in this article are divided between observational studies that investigated the relationship between intake/serum levels of fatty acids and asthma in children receiving unmodified diets and interventional studies that examined the additive effects of diets supplemented with omega-3 fatty acids.

OBSERVATIONAL STUDIES ON THE INFLUENCE OF CONSUMPTION OF LCPUFAS ON ATOPIC DISEASES

Most of the evidence that gave rise to the hypothesis that *n*-3 PUFA may have a beneficial therapeutic effect on asthma came from observational studies^{32–36} that showed a protective role after the regular consumption of fish, the major source of *n*-3 fatty acids in the diet. Of all of the outcome observational studies with asthma reviewed, only 13 were identified. Of these, eight studies showed a beneficial effect, two studies showed a negative association, and three showed no association. Of the studies that found a beneficial association between fish intake during infancy and childhood and asthma, two were prospective cohorts, two were case-control, and four were cross-sectional, respectively. The reduction in asthma risk due to the fish intake among the studies ranged between 22 and 74%. All three prospective cohort studies and the cross-sectional studies of Antova *et al.*³⁷ and Kim *et al.*³⁸ used a parental questionnaire to determine the time point of fish introduction during the 1st year of life.

Recent studies have shown the positive effects of omega-3 PUFA supplementation on bronchial asthma in childhood and the relationship between the increased incidence of childhood obesity and the role of omega-3 PUFA in reducing the metabolic and vascular alterations induced by the fat accumulation since young age (Table 1). However, it is well established that further studies are needed to endorse the promising results outlined by literature analysis. Increasing evidence suggests that fish, fish oil, or LCPUFA intake during pregnancy, lactation, and early postnatal years improves respiratory health and have effects on allergic and infectious respiratory illnesses including reductions in asthma and other allergy manifestations or markers.³⁹

In the other studies reviewed, semiquantitative Food Frequency Questionnaires (FFQs) or parental report of fish consumption without frequencies were used. Only in the study of Kull⁴⁰ was fish consumption frequency collected. The ideal method of collecting information on fish consumption is by parental FFQ using various food categories and consumption frequencies.

The most beneficial effect of fish intake on asthma were reported by Hodge *et al.*,⁴¹ which was greater than that reported in all of the other studies (odds ratio [OR] = 26%; 95% CI, 0.09–0.72; $p < 0.01$). This clinical trial was conducted in children between the ages of 8 and 11 years. In this study the type of fish, *i.e.*, fresh oily fish (>2% fat), led to a greater reduction of asthma risk, even after adjustment for confounding factors, than total fish consumption (OR = 26% versus OR = 52%, respectively). A possible explanation of these findings could be attributed to the greater content of omega-3 fatty acids in oily fish than in nonoily fish.

A cross-sectional multicenter study of Antova,³⁷ conducted on 20,271 children from six central and eastern European countries (age range, 7–11 years) showed that low fish intake (<1/mo) remained a significant independent predictor of persistent cough (OR = 1.18; 95% CI, 1.04–1.34; $p = 0.01$), wheeze ever (OR = 1.14; 95% CI, 1.03–1.34; $p = 0.01$), and current wheeze (OR = 1.21; 95% CI, 1.06–1.39; $p = 0.01$) in a fully adjusted model. The main strengths of this study were the inclusion of a large sample size and a diverse population. One of the limitations is that fish intake frequency was classified only in two categories, more or less than once per month.

A Swedish study³⁸ that included 1014 children aged between 5 and 14 years confirmed, as did the two previous studies, a protective role of fish intake on asthma, showing less physician-diagnosed asthma and less current asthma in children who frequently consumed fish. This study included five food frequency categories (ranging from everyday consumption to none); however, the type of fish consumed was not identified. The authors also found that children con-

suming higher quantities of polyunsaturated oils had more often wheeze ($p < 0.05$), and those consuming more olive oil had fewer bouts of doctor-diagnosed asthma ($p < 0.05$). The association, however, was significant only excluding children with food allergies. The authors have no explanation for this finding.

Takemura *et al.* reported a positive association between fish consumption and risk of asthma in 6- to 15-year-old children in the Tokorozawa Childhood Asthma and Pollinosis Study.⁴² This study population included 1673 currently asthmatic children and 22,109 controls. The results showed that children who have fish one to two times a week had a higher prevalence of asthma than those who have fish one to two times a month. Moreover, the risk increased gradually with increasing the frequency of fish intake. Authors did not differentiate the different types of fish intake. Another confounding factor could be that in Japan fish is often eaten fried, and larger quantities of polyunsaturated oils containing high quantities of omega-6 are used.⁴³ Similarly, in the study of Huang⁴⁴ conducted on 1166 adolescents, a positive association between higher intake of oily fish and higher prevalence of doctor-diagnosed asthma was found with a univariate analysis.

Of the three studies that reported no association between dietary fish intake and asthma, two were prospective cohort studies and one was a case-control study. The Italian study by Farchi *et al.*⁴⁵ evaluated the relationship between diet and occurrence of wheeze, shortness of breath, and allergic rhinitis symptoms and found no association between consumption of fish and asthmatic symptoms. Similarly, the Dutch study found no association between fish intake and recent occurrence of asthma or recent onset of wheezing in a group of 2978 2-year old children, in a follow-up period of 1 year.⁴⁶ Both studies used a parental/maternal FFQ. The first study specifically considered also the intake of oily fish and pasta with oily fish, whereas the second study only considered general fish consumption. However, both of these prospective studies did not include monthly fish consumption frequencies in their analysis, but considered only weekly consumption frequencies, which could have obviated the identification of significant associations. In the case-control study of Hijazi *et al.*⁴⁷ the FFQ responses to questionnaires were obtained directly from the group of children studied that could have led to misclassification of atopic outcomes.

Olive oil has a content of LA (18:2n-6) and of oleic acid (18:1n-9) that are the lower and higher than the other vegetal polyunsaturated oils, respectively. A reduced percentage of AA would be expected if oleic acid inhibits δ -6 desaturases, elongase-5, and/or δ -5 desaturase, the enzyme governing formation of AA from LA. Based on results of a cross-sectional human study and cells culture experiments, Hostmark and

Table 1 Summary of the studies concerning omega-3 supplementation during infancy/childhood and asthmatic outcomes

Author	Year	Subjects (study nos.)	Source of Fatty Acids Supplementation	Duration	Effects/Observations	Reference
Hodge	1998	39	0.72 g/day of EPA and 0.48 g/day of DHA, plus canola oil and canola-based margarines vs omega-6 supplementation	6 mo	No significant changes in clinical outcome measures	52
Nagakura	2000	29	Oil capsules containing 84 mg of EPA and 36 mg of DHA given at the dosage of 17.0–26.8 mg/kg for EPA and 7.3–11.5 mg/kg for DHA versus placebo	Intervention study, 10 mo	Asthma symptom scores decreased and responsiveness to acetylcholine decreased in the fish oil group but not in the control group	53
Almqvist	2007	516	Tuna fish oil supplement, omega-3-rich margarines and cooking oils vs placebo	Intervention study, 5 yr	Wheeze ever, doctor visits for wheeze, bronchodilator use, and nocturnal coughing were significantly reduced in children in the higher exposure quintiles; no difference in diagnosed asthma or atopy between the exposure quintiles	51
Al Biltagi	2009	60	One capsule/day containing $1 \times g$ of a triglyceride oil (containing approximately EPA-DHA 30%), 1 capsule/day containing 15 mg of Zn and 1 capsule/day containing 200 mg of ascorbic acid vs placebo	38 consecutive wk	There was a significant improvement of C-ACT, pulmonary function tests and sputum inflammatory markers with diet supplementation with omega-3 fatty acids, vitamin C and Zn; there was also significant improvement with the combined use of the three supplementations than single use of any one of them	54

C-ACT = Childhood Asthma Control Test; DHA = docosahexaenoic acid; EPA = eicosapentaenoic acid.

Lunde suggested that oleic acid could be one of the cheese factors with desaturase-inhibiting properties.⁴⁸ These findings seem to be in accordance with a previous study showing a decrease in AA, in response to ingesting 25 mL of olive oil per day for 3 weeks.⁴⁹ Additionally, oleic acid seems to be a weak competitive inhibitor of cyclooxygenases,⁵⁰ which catalyzes conversion of the C20 PUFAs AA and EPA into prostaglandins, thromboxanes, and leukotrienes.⁵⁰ These findings not only could explain the results of the study by Kim but also suggest the need for further investigation of the effects of the polyunsaturated oils and olive oil in clinical trials.

INTERVENTION STUDIES ON LCPUFAS AND ASTHMA IN CHILDREN: PREVENTION AND TREATMENT

A second group of studies examined in this study are intervention studies conducted in children whose diets were supplemented with omega-3 fatty acids. Randomized controlled trials (RCTs) or experimental/intervention studies include designs that provide the highest level of testing of cause and effect; they are considered the standard for investigating questions of treatment efficacy or effectiveness.^{51,52} Here, we consider the RCTs that considered clinical outcome; therefore, we excluded the studies of Vaisman⁵³ and Damsgaard⁵⁴ that did not report clinical outcomes but only blood immune markers. The Childhood Asthma Prevention Study, a single-blinded study, considered children at risk of developing asthma because of family history. Omega-3 supplementation was started from 6 months of age or earlier if the infant was fed with formula. Tuna oil was given in capsules in doses related to the age of infant/children. At the highest possible doses, infants received 3.6 mg of DHA and 0.8 mg of EPA per kilogram of body weight. Blinded assessments were conducted at 18 months and 3 and 5 years of age.⁵⁵ The duration of supplementation was 5 years. At 18 months of age, a decreased prevalence of wheeze in the fish oil group was observed and higher plasma levels of LCPUFA omega-3 were associated with lower bronchodilator use, irrespective of the supplementation group (intervention group versus placebo).⁵⁶ However, no significant effects of fish oil were observed on any of the clinical outcome measures relating to lung function, allergy, or asthma at 5 years of age.⁵⁷ The authors pointed out that there could be a potential for effect attenuation in this study and that measurement error in the dietary assessments and the infrequent plasma measurements might have limited the ability to detect an association between fatty acid exposures and outcomes. Few RCTs evaluated the role of LCPUFA

supplementation in the treatment of bronchial asthma in children and they gave contrasting results.

Hodge *et al.*⁵⁸ have shown that in a group of 39 Australian asthmatic children aged between 8 and 12 years, supplementation with omega-3 compared with administration of omega-6 determined a significant increase in serum levels of EPA and decrease of the TNF- α and of the circulating eosinophils compared with the "prenutritional intervention" phase. However, there were no significant effects on the clinical severity of asthma. It should be stressed, however, that the supplementation dose used in this study (0.72 g/day of EPA and 0.48 g/day of DHA, plus canola oil and canola-based margarines) was comparable (if not superior) with those used in other studies in which there were found beneficial effects. Nagakura *et al.* conducted a randomized double-blind placebo-controlled trial to evaluate the effects of long-term (10 months) dietary supplementation with fish oil (oil capsules containing 84 mg of EPA and 36 mg of DHA) in 29 children (range of age, 4–17 years) with bronchial asthma, exposed to the same type of respiratory and food allergens. The dosage varied depending on the weight of the subject, being 17.0–26.8 mg/kg for EPA and 7.3–11.5 mg/kg for DHA. The results of this trial showed a significant increase in EPA serum concentration only in the fish group, with a significant decrease in both asthma symptoms (in terms of score) and responsiveness to acetylcholine in the fish oil group, but not in the control group. However, there were no significant changes in terms of forced expiratory volume in 1 second between the two groups. These data suggest that long-term supplementation with fatty acids of the omega-3 series (EPA and DHA) may cause a decrease in bronchial inflammation, without changing airway caliber.⁵⁹ The results of the Nagakura study suggest that in a controlled environment, supplementation of LCPUFA may be beneficial for asthma severity.

A recent randomized, double-blind, placebo-controlled study investigated the effect on 60 moderate-persistent asthmatic children aged between 7 and 10 years of the supplementation with a combination of omega-3, zinc, and vitamin C. In the treatment group an improvement of subjective symptoms and pulmonary function tests and a reduction of the amount of sputum inflammatory markers were observed. The authors speculate that zinc and vitamin C may reduce the production of inflammatory mediators determining an antioxidant action, which, in turn, would enhance the anti-inflammatory effect induced by zinc itself and omega-3 fatty acids.⁶⁰

DISCUSSION

The results of the present study suggest a diversity of responses to omega-3 supplementation and asthma.

The intriguing question to be answered is why did a lower dose of LCPUFA used in the Japanese trial significantly improve asthma control while the higher doses used in the Australian study showed no effect? One of the plausible explanations is that other dietetic factors, besides to *n*-3 PUFAs, could be responsible for the contrasting results of the intervention trials. It is important to recognize that Japanese diet is low in saturated fatty acids and rich in short-chain fatty acids.⁶¹ Because it is well-recognized that a high dietary intake of saturated fatty acids inhibit δ -6 desaturase⁶² and that short-chain fatty acids have an important role in resolution of inflammation and immune regulation,⁶³ both of these variables together with omega-3 supplementation could have provided an anti-inflammatory effect that could have led to the control of the asthma symptoms. Although the formulation of supplementation does not appear to have given a complete explanation for the aforementioned observed results, this variable needs further investigation in future intervention trials because it is still unclear which combinations of omega-3 fatty acids should be the better to use for the supplementation.

Another possible explanation for the discordant results of the Japanese and Australian studies is the "genetic hypothesis." The considerable difference in the response to lipid supplementation of the individuals with asthma could be related to genetic factors. This variability seems to be closely related to the capacity of omega-3 to change the leukotriene profile, and this would seem to have a genetic origin. Okamoto *et al.*⁶⁴ have shown that only a subset of asthmatic patients benefited from a supplementation with a vegetable source of *n*-3 PUFA and that the leukocytes of these individuals reduced their secretion of C4 after the period of supplementation. Several genes may be involved in the regulation of fatty acids and lipid levels and nutritional influences may play an important role as well. Therefore, the analyses of important gene variants, *e.g.*, FADS gene variants, should be included in any future intervention study to thoroughly investigate the effects of LCPUFA supplementation. Additionally, recent gene–nutrition interaction studies suggest that FADS genotype may be also important for the development of atopic diseases outcomes. Standl *et al.* assessed the influence of FADS1 FADS2 gene cluster polymorphisms on the association between dietary fatty acid intake and atopic diseases and allergic sensitization in 10-year-old children.⁶⁵ The authors found no significant association between the six FADS single nucleotide polymorphisms and allergic diseases or atopic sensitization. However, daily margarine intake was significantly associated with asthma in individuals carrying the homozygous major allele. This association was also significant after correcting for multiple testing. These findings might explain the partly inconsistent results on dietary

fatty acids and allergic diseases in the observational studies and outlines the importance of including genetic data also in such studies.

CONCLUSIONS

After reviewing these studies it may not be possible to definitively recommend a modification of omega-3 LCPUFA dietary intake or supplementation with omega-3 LCPUFA with the aim to treat or to prevent asthma in clinical practice. A definitive conclusion can not be made supporting a beneficial effect of dietary modification or supplementation with omega-3 to the prevention or modification of asthmatic diseases in children. It is clear that additional research in this field is required, in particular, the role of diet during early life and the issue of individual susceptibility. The analyses of FADS gene variants should be included into the observational and intervention studies to thoroughly investigate the effects of LCPUFA supplementation. If the variations in terms of susceptibility to supplementation are confirmed and are characterized in future studies, it may be possible to treat with PUFA only susceptible individuals. Future research is necessary to establish the efficacy of dietary manipulation as part of the treatment of asthma in children.

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