A systematic review of the association between fish oil supplementation and the development of asthma exacerbations

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Abstract

A systematic review was conducted to examine the association between fish oil supplementation and the development of asthma exacerbations. Comprehensive literature reviews of recent fish oil studies were performed to evaluate alterations in asthma surrogate markers. Additionally, the relative compositions of the fish oils used in each study were analyzed. The results of the review were inconclusive, but provide a basis for future research methods.

Keywords

Allergy/immunology, fish oil, asthma

Introduction

Could an over-the-counter supplement as simple as fish oil be the key to preventing asthma exacerbations? Studies have explored the connection between the omega-3 fatty acids contained within fish oil and a variety of chronic inflammatory conditions, including asthma, cardiovascular disease, and rheumatoid arthritis. Reviews of fish oil research relating to asthma have not shown statistical significance when assessing the effect of fish oil intake in the development of asthma exacerbations, except that an inverse relationship appears to exist between expectant mothers' and infants' intake of fish and the development of childhood asthma.[1] With an unlimited variety of fish oil formulations available for consumer purchase, from regular fish oil to cod liver oil and krill oil, it is important to examine the components of these formulations to determine if the potential benefits achieved from supplementation vary based on the fish oil variety. This notion is underscored by the polarizing results presented in the PCSO-524™ and MAG-EPA trials versus the HUNT study.[2–4] In the PCSO-524 trial, there was a statistically significant amelioration in asthma symptoms and surrogate asthma markers in study subjects after the use of a specialized supplement containing a variety of oils, including olive oil, docosahexaenoic acid (DHA), and eicosapentaenoic acid (EPA).[2] The MAG-EPA study, which included the use of an EPA derivative, produced similar favorable results in asthmatic participants.[3] Conversely, results of the Norwegian HUNT study revealed that pre-1999 Norway cod liver oil was fortified with high concentrations of vitamin A, which may have led to the development of chronic inflammatory diseases, including asthma.[4] This result is especially relevant today as several of the leading US cod liver oil products contain relatively higher amounts of vitamin A per serving than those shown to have potentially resulted in the negative effects observed in the HUNT study.[4] Given this, it is important to understand the correlation between fish oil and asthma, with special attention paid to the composition of the fish oil formulation before safety and efficacy recommendations can be made to the consumers.

Asthma suffers totaled approximately 25 million in the United States in 2011 with the incidence rate growing each year.[5] Annual medical expenses related to asthma exacerbations were approximately US$50.1 billion in 2007.[5] Of the

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risks associated with the development of asthma, the main risk factors include age, race, and gender.[5] Comparing the age-related risks, children are slightly more afflicted than adults (57% vs 51%, respectively).[5] The highest incidence of asthma, based on racial/ethnic groups, is attributed in non-Hispanic Blacks (11% in adults and 17% in children).[5] The mainstay of treatment for asthma is currently focused on prevention, including avoidance of environmental triggers and regular pharmacological therapy.[5] Common asthma triggers include upper respiratory viral infections, exposure to mold, outdoor air pollution, and tobacco smoke.[5] Current pharmacological treatments include inhaled corticosteroids, leukotriene antagonists, and long-acting beta-adrenoceptor agonists.[5] If an inverse relationship exists between fish oil supplementation and the development of asthma exacerbations, in the future, fish oil may be used as an adjunct prevention treatment for asthmatics.

Most fish oil supplements are comprised of omega-3 polyunsaturated fatty acids (n-3 PUFA), namely EPA and DHA.[6] EPA competitively inhibits the incorporation of arachidonic acid (AA), an omega-6 polyunsaturated fatty acid (n-6 PUFA), into cellular membranes.[6] This results in a greater ratio of EPA metabolites, which are less potent inflammatory mediators than those derived from AA.[6] Eicosanoid metabolites that are particularly influential in pulmonary immunologic responses are leukotrienes.[7] Downstream metabolites of both AA and EPA, leukotrienes are produced by leukocytes, macrophages, mastocytoma cells, and platelets in response to allergens and other stimuli.[7,8] Leukotrienes give rise to inflammatory mediators that are involved in many hypersensitivity reactions and inflammatory responses, including those observed in asthma exacerbations.[7]

To date, adult studies of fish oil supplementation in asthma have been relatively inconclusive.[1,9] Reisman et al.'s[9] systematic review researched the effect of omega-3 fatty acids in the treatment and prevention of asthma exacerbations. The review included randomized controlled trials of literature published prior to April 2003. The review focused on trials with subjects of any age that used dietary supplementation or pharmacological supplementation with omega-3 as treatment or prevention of asthma symptoms.[9] Forced expiratory volume (FEV1) was the primary outcome studied, but Reisman et al.[9] examined other respiratory outcomes and inflammatory mediators as well. The overall results were inconclusive due to the inconsistent results reported in these trials, and the authors concluded more research was needed, including a more defined source of the omega-3 constituents included in these studies.[9] Since 2003, several studies in children have shown promising results reflecting a reduction in the development of childhood asthma after infants were supplemented with fish oil, either via breast milk or direct means.[1] The purpose of this systematic review is to determine whether new studies reveal an inverse relationship between fish oil supplementation and the development of asthma exacerbations. Furthermore, this review will examine the varying formulations of fish oil supplementation used in the studies examined to determine if EPA:DHA ratios may contribute to a trend in observed results.

Methods

The systematic scientific literature search for this reporting included the EBSCO database, using the following search algorithm: ((PUFA or omega-3 or omega 3 or fish oil) and (asthma or asthmatic)) from 1 January 2013 to 25 July 2015. A second search was performed using the PubMED database with the following search algorithm: ((fish oil or PUFA or omega-3 or omega 3) AND (asthma or asthmatic)) since 1 January 2013 (last search date: 25 July 2015). All available literature was searched, which yielded 93 unique references. These references were screened independently by two researchers for full-text review based on population, form of n-3 PUFA tested, and subject disease state. Inclusion parameters required direct, oral administration of fish oil supplementation (i.e. breast milk transmission of fish oil was excluded), randomized control trials, in vivo studies, studies involving asthma-specific surrogate markers or endpoints, and studies that used a formulation of fish oil with the main components of DHA and/or EPA. References from identified studies were screened by title or abstract for inclusion based on the a priori inclusion parameters applied to the original search articles. Discrepancies were resolved by group discussion. All studies were assessed for potential bias based on funding or author affiliations. EPA:DHA ratios were typically reported as whole numbers to maintain continuity (i.e. EPA:DHA of 2.5:1 was reported as 2.5).

Results

Tumor necrosis factor-α

Serum concentrations of the inflammatory cytokine, tumor necrosis factor (TNF)-α, were tested by Miranda et al.[10] in rats (unreported EPA:DHA ratio) and by Schuster et al.[11] in mice (DHA, only; EPA, only; and 1:1, EPA:DHA formulations). Miranda et al.'s[10] study reflected no significant difference in TNF-α levels among fish oil or placebo groups. However, Schuster et al.'s study showed significantly lower TNF-α concentrations in all three n-3 PUFA groups tested as compared to the control group. Schuster et al.[11] also demonstrated that the EPA component of fish oil is a more potent inhibitor of TNF-α when compared to the sole-DHA group Figure 1 and Table 1).

Pulmonary mucus deposition

Lung mucus deposition was evaluated in the models by Bargut et al.[12] in mice (1.075 EPA:DHA ratio) and Miranda et al.[10] in rats (unreported EPA:DHA ratio). Bargut et al.'s[12]
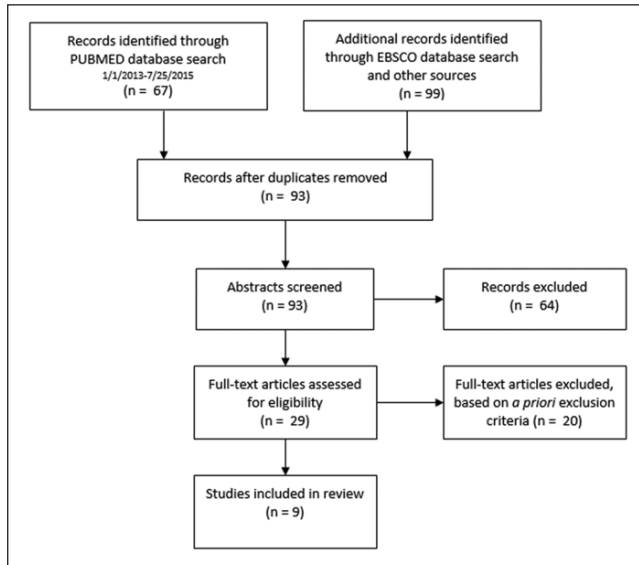
Figure 1. Study selection.

study reflected significantly attenuated mucus production in the ovalbumin (OVA)-exposed fish oil group when compared to the OVA-exposed control group (p<0.0001). However, Miranda et al.'s[10] study showed no significant change in airway mucus levels between the fish oil and control groups.

Eosinophil pulmonary infiltration percentage

Eosinophil infiltration levels were included in the mice studies by Bargut et al.[12] (1.075 EPA:DHA ratio), Eliaçik et al.[14] (2.5 EPA:DHA ratio), and Schuster et al.[11] (DHA, only; EPA, only; and 1:1, EPA:DHA formulations) and by Brannan et al.[17] in humans (2.0 EPA:DHA ratio). Bargut et al.'s[12] study demonstrated a significantly reduced eosinophilic response in the OVA-exposed fish oil group when compared to the OVA-exposed control group. Eliaçik et al.'s[14] study showed no significant difference in eosinophil concentration ratios between groups. Schuster et al.'s[11] study showed that DHA, alone, produced significantly higher levels of bronchoalveolar lavage fluid (BALF) eosinophils than all other groups (p<0.001), but did not show a significant difference in eosinophil levels between the control and the other n-3 PUFA groups. In Brannan et al.'s[17] human study, no significant sputum eosinophil differences were observed in either group.

Production of T-cell cytokines

Bargut et al.[12] (1.075 EPA:DHA ratio) and Schuster et al.[11] (DHA, only; EPA, only; and 1:1, EPA:DHA formulations) studied cytokine production in mice. In Bargut et al.'s[12] study, interleukin (IL)-4, IL-5, IL-13, IL-17, eotaxin 1, and eotaxin 2 production were significantly reduced in the fish

oil group (p<0.05). In addition, nuclear factor kappa-B (NFκB) levels were significantly reduced in the OVA-exposed fish oil group when compared to the OVA-exposed control group (p=0.0006).[12] There were no significant differences in interferon (INF)-gamma or IL-10 levels in either OVA group.[12] GATA-3 production was increased in both OVA groups, but the increased levels were attenuated by 59% in the fish oil supplementation group when compared to the control (p=0.0162).[12] Finally, peroxisome proliferator-activated receptor gamma (PPARγ) production was 98% higher in the fish oil group (p<0.0001).[12] In contrast to Bargut et al.'s study, Schuster et al.'s[11] study showed no significant differences among the two cytokine levels studied, IL-5 or IL-10, in the fish oil or control groups.

Lung composition alterations

Bargut et al.[12] (1.075 EPA:DHA ratio), Miranda et al.[10] (unreported EPA:DHA ratio), Eliaçik et al.[14] (2.5 EPA:DHA ratio), and Schuster et al.[11] (DHA, only; EPA, only; and 1:1, EPA:DHA formulations) all studied the components of the lung to determine the alterations post-exposure to an irritant to determine if the use of fish oil affected the composition of pulmonary structures. In Bargut et al.'s[12] mice study, results showed a significant reduction in peribronchiolar matrix deposition post-antigen exposure (p=0.0099). In addition, the use of fish oil reduced antigen-induced lung hyperreactivity (p<0.05).[12] Miranda et al.'s[10] rat model demonstrated a significant increase in static lung compliance in fish-oil supplemented, asthmatic rats (p<0.05); however, there was no significant variation between the post-exposure groups in pulmonary smooth muscle force of contraction or smooth muscle layer thickness. Eliaçik et al.'s[14] model found that basement membrane thickness was significantly lowered after fish oil supplementation (p=0.038), but found no significant difference in goblet cell numbers or subepithelial smooth muscle thickness of airways between the groups. On comparing lung airway resistance, Schuster et al.'s[11] study of varying formulations of EPA and DHA in mice showed that the sole-DHA diet produced significantly higher resistance measurements than all other groups.

Triglyceride levels

Triglyceride levels were reported in the human studies conducted by Ade et al.[13] (1.5 EPA:DHA ratio) and Brannan et al.[17] (2.0 EPA:DHA ratio). In Ade et al.'s[13] study, participants consumed a high-fat meal after 3-week supplementation of fish oil or placebo. Blood triglycerides significantly increased in both groups after the high-fat meal (p<0.05), which significantly correlated to the fractional exhaled nitric oxide (FE_{NO}) in the control group (p<0.05).[13] However, the fish oil group resulted in a comparatively reduced FE_{NO} (p<0.05).[13] The only significant result from Brannan et al.'s[17] study was a 27% reduction in blood triglyceride

Table 1. Summary of findings.

Study	EPA:DHA ratio	Population	Significant findings compared to control group
Bargut et al.[12]	1.075	Mice	Increased PPARγ expression in saline-FO ($p < 0.0001$) and OVA-FO ($p < 0.0001$) groups; attenuated elevations of NFκB ($p = 0.0006$) and GATA-3 ($p = 0.0410$) expression in OVA-FO group; attenuated elevations of IgE (~64%, $p = 0.0078$), IgGl (~83%, $p < 0.0001$), IL-4 (~60%, $p = 0.0004$), IL-5 (~50%, $p = 0.0002$), IL-13 (~47%, $p = 0.0042$), IL-17 (~34%, $p = 0.0072$), eotaxin-1 (~23%, $p = 0.0212$), eotaxin-2 (~35%, $p = 0.0004$), total BALF leukocyte infiltration (~52%, $p = 0.0002$), BALF mononuclear cells ($p = 0.0029$), BALF neutrophils ($p < 0.0001$), BALF eosinophils ($p = 0.0002$), peribronchiolar matrix deposition ($p = 0.0099$), mucus deposition (~72%, $p < 0.0001$), and AHR ($p < 0.05$) in OVA-FO group
Miranda et al.[10]	Not reported	Rats	Static lung compliance increased in asthmatic rats following fish oil supplementation ($p < 0.05$). No significant findings in BALF eosinophilia, concentrations of TNF-α and IL-IB in airway tissues, mucus deposition, or force of contraction post-Ach
Ade et al.[13]	1.5	Humans	Attenuated elevation of FE_{N0} in FO versus placebo group ($1.99\% \pm 10.5\%$ vs $25.7\% \pm 16.7\%$, respectively, $p < 0.05$)
Eliacik et al.[14]	2.5	Mice	Reduced BALF neutrophils ($p = 0.024$) and mean basement membrane thickness ($p = 0.038$) No significant findings in lymphocyte, macrophage and eosinophil percentages, goblet cell numbers, subepithelial smooth muscle of airways, and bronchial-associated lymphoid tissue
Schuster et al.[11]	DHA, only EPA, only 1:1 EPA/DHA	Mice	DHA, only: increased BALF eosinophils ($p < 0.05$), IL-6 levels ($p < 0.05$), lung resistance measurements, and BALF oxylipin total concentrations Decreased TNF-α ($p < 0.05$) and plasma concentration of total oxylipins EPA, only: decreased TNF-α ($p < 0.05$) and AA-derived BALF oxylipins 1:1 DHA/EPA: decreased TNF-α ($p < 0.05$) No significant findings in IL-5, IL-10, or eotaxin in any of the FO groups
Zanatta et al.[15]	1.25	Rats	Lower concentrations of nitrite (~30%, $p < 0.005$), catalase activity ($p < 0.001$), and lipid hydroperoxide (~40%, $p < 0.001$) Increased concentrations of superoxide dismutase (40%, $p < 0.05$) and glutathione peroxidase ($p < 0.05$). No significant findings in PAF biologic activity in lung tissue or leukocyte concentrations
Head and Mickleborough[16]	DHA, only	Humans	No significant findings in FEV1, EBC pH, 8-isoprostane, protectin Dl, and 17S-hydroxy docosahexaenoic acid
Brannan et al.[17]	2.0	Humans	Decreased fasting blood triglyceride levels (~27%, $p < 0.001$) No significant findings in BHR to mannitol, sputum counts, or urine mast cell mediators
Lundström et al.[18]	2.0	Humans	Decreased average sum of ALA oxylipin metabolites ($n = 4$, $p = 0.022$), increased average sum of EPA oxylipin metabolites ($n = 5$, $p = 0.0051$), and increased average sum of DHA oxylipin metabolites ($n = 5$, $p = 0.00018$)

DHA: docosahexaenoic acid; EPA: eicosapentaenoic acid; PPARγ: peroxisome proliferator-activated receptor gamma; FO: fish oil; OVA: ovalbumin challenged; NF: nuclear factor; Ig: immunoglobulin; IL: interleukin; BALF: bronchoalveolar lavage fluid; AHR: antigen-induced hyperreactivity; TNF-α: tumor necrosis factor alpha; Ach: acetylcholine; FE_{NO}: fraction of exhaled nitric oxide; FEV1: forced expiratory volume in 1 s, EBC: exhaled breath condensate; BHR: bronchial hyperresponsiveness; ALA: alpha-linolenic acid.

levels in fasting fish oil participants compared to placebo ($p < 0.001$).

Oxidative stress

Zanatta et al.'s[15] (1.25 EPA:DHA ratio) study was the only study that measured markers of oxidative stress, namely, BALF nitrite, lipid hydroperoxide, superoxide dismutase, and glutathione peroxidase. Fish oil supplementation significantly lowered the concentrations of both BALF nitrite (~30%, $p < 0.005$) and lipid hydroperoxide (~40%, $p < 0.001$) in asthmatic rats.[15] Furthermore, increased antioxidant levels

of superoxide dismutase (~40%, $p < 0.05$) and glutathione peroxidase (13-fold increase, $p < 0.05$) were observed in the fish-oil asthma group as compared to the control group.[15] Fish oil also resulted in significantly lower catalase activity ($p < 0.001$) in non-asthmatic rats.[15]

Metabolic profile

The human studies of Lundström et al.[18] (2.0 EPA:DHA ratio) and Head et al.[16] (DHA, only) and the mice study of Schuster et al.[11] (DHA, only; EPA, only; and 1:1, EPA:DHA formulations) measured downstream oxylipin metabolites in

fish oil and control groups. Lundström et al.'s[18] serum study quantified lipid mediators by pathway, namely, the cyclooxygenase (COX), lipoxygenase (LOX), and cytochrome P450 (CYP) metabolic pathways. As expected, a significant increase in EPA and DHA-derived mediators and a significant decrease in AA-derived mediators were observed in the fish oil group.[18] In Head et al.'s[16] study, exhaled breath condensate components were tested for 8-isoprostane, DHA metabolites, 17S-hydroxy docosahexaenoic acid, and protectin D1. The results showed no significant differences between the DHA and control groups.[16] Schuster et al.'s[11] study showed that plasma AA-derived oxylipins were significantly lower in the DHA-only supplement group when compared to the EPA and DHA combination group. However, after the OVA challenge, AA-derived oxylipins in BALF were significantly lower in only the EPA and DHA combination group when compared to placebo.[11]

Peroxisome proliferator-activated receptor-γ expression

Bargut et al.'s[12] study of mice (1.075 EPA:DHA ratio) revealed increased expression of the anti-inflammatory mediator, PPARγ in both fish oil groups ($p < 0.0001$) when compared to the control group.

Discussion

Although the study results appear contradictory, a potential correlation between inflammatory mediators and the use of fish oil that varies based on the EPA:DHA ratio of the fish oil is noted. For example, Schuster et al.'s[11] DHA-only study showed significantly increased inflammatory mediators compared to placebo, which was not reflected in any of the studies that contained EPA. Furthermore, the DHA-only group showed no significant anti-inflammatory benefit other than a reduction in TNF-α.[11] The second DHA-only study conducted by Head showed no significant findings in the markers tested.[16] These results suggest that DHA, when administered unopposed by EPA, not only precludes protection against inflammatory responses as compared to EPA formulations, but may also ultimately result in increased inflammation.

Each of the combined EPA formulation studies that tested anti-inflammatory mediators showed statistically significant anti-inflammatory responses in the fish oil groups as compared to placebo. None of the studies reported adverse effects or significant increases in inflammatory mediators in relation to placebo. However, some of the results were comparatively inconsistent based on the testing of similar markers. For example, Eliaçik et al.'s and Bargut et al.'s studies found differing statistical significance in BALF eosinophil concentrations, with Bargut et al. showing a reduction in eosinophils and Eliaçik et al. finding no change in eosinophil concentrations between groups.[12,14] Eliaçik et al.'s[14] study

showed the highest EPA:DHA ratio of 2.5, which may have contributed to an overall lack of significant findings other than reduced BALF neutrophils and a reduction in mean basement membrane thickness. These combined results infer that the EPA:DHA ratio is not only important but also essential in determining whether a correlation exists between fish oil supplementation and asthma exacerbations. Fish oils with higher DHA than EPA concentrations appear to be ineffective in relieving inflammation. On the other hand, ratios of EPA:DHA that were at least 1, but less than 2.5, did reveal promising results in reducing inflammation via the surrogate markers tested. Therefore, to determine whether an association exists between the use of fish oil and asthma exacerbations, it is important that future studies maintain consistency in the EPA:DHA ratio used so that study results can be combined and examined based on a foundation of similar methodology.

A notable limitation to this review is the narrow inclusion of only four human studies, which were widely varied in study design. Brannan et al.'s[17] double-blind, crossover trial of asthmatic subjects utilized inhaled mannitol to induce asthma symptoms that were measured by FEV, sputum eosinophils, spirometry, Asthma Control Questionnaire (ACQ) scores, and lipids after 3 weeks of fish oil supplementation. Lundström et al.'s[18] double-blind, crossover study focused on the varied serum oxylipin measurements in asthmatic patients treated with fish oil for 3 weeks. Head et al.'s[16] double-blind, crossover trial focused on exercise-induced asthma symptoms in asthmatic patients. Finally, Ade et al.'s[13] randomized, single-blind trial included healthy, non-asthmatic participants treated with high-fat dairy meals to induce airway inflammation after a 3-week supplementation with fish oil.

Although each of the human study designs varied, cumulatively, a basis for exploring the many aspects of asthmatic symptoms and progression is provided. As to how the combined studies are to be interpreted for use by asthmatics seeking a prophylactic treatment to ameliorate pulmonary inflammation, unfortunately, conclusive and standardized supplementation and outcome data are still lacking. This is especially true as it pertains to consistent fish oil formulations (EPA:DHA ratio) and consistent measurements of asthma symptoms, such as the ACQ scoring system or FEV. Given the nature of fish oil supplementation and its limited adverse drug reaction profile, the benefits of conducting a standardized set of trials appear to outweigh the potential risks in the future examination of fish oil supplementation's effect in ameliorating pulmonary inflammation.

Conclusion

The results of this review are inconclusive, requiring further studies to determine whether an association exists between fish oil supplementation and the development of asthma exacerbation. The examined fish oil studies that showed the

most anti-inflammatory benefit by way of asthma surrogate markers contained an EPA:DHA ratio of not less than 1:1, but no more than 2.5:1.

Declaration of conflicting interests

Ethical approval

Ethical approval was not sought for this study because the study was a systematic review with no research subjects.

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