Agency for Healthcare Research and Quality

Evidence Report/Technology Assessment

Number 91

Health Effects of Omega-3 Fatty Acids on Asthma

Summary

Introduction

The purpose of this study was to conduct a systematic review of the scientific medical literature to identify, appraise, and synthesize the evidence for the health effects of omega-3 fatty acids on asthma. The review was requested and funded by the Office of Dietary Supplements, National Institutes of Health. It was undertaken as part of a consortium involving three Evidence-based Practice Centers (EPCs) currently investigating the value of omega-3 fatty acid supplementation across 11 health/disease areas. The three EPCs are Southern California/RAND, Tufts-New England Medical Center, and the University of Ottawa (UO) EPC. To ensure consistency of approach, the three EPCs collaborated on selected methodological elements, including literature search strategies, rating of evidence, and data table design.

Asthma is a chronic inflammatory disorder of the airways leading to airways hyper-responsiveness and associated symptoms such as wheezing and coughing, and is also typically associated with widespread but variable airflow obstruction that is often reversible either spontaneously or with treatment.[1] The inflammatory process is a complex one, involving a multitude of cell types and activities marking the early and late phase asthmatic responses.[2] There are important issues requiring careful consideration in diagnosing asthma, including the need to distinguish it from transient wheezing disorders in children, especially under the age of 5 years, and also from chronic obstructive pulmonary disorder, especially in older adults who are current or ex-smokers.[3,4]

Various strategies have been developed to manage asthma. Since airway inflammation is multifactorial, involving various cell types and mediators, the drugs used to decrease inflammation may act at several different steps in the inflammatory process.[1,3] Agents that modify the asthma process, with some influencing inflammation, include: beta-2 adrenergic agonists, corticosteroids, leukotriene modifiers, mast-cell stabilizing agents, and theophylline.

Considerable interest in the possible value of omega-3 fatty acid supplementation in asthma was sparked by Horrobin's hypothesis that the low incidence of asthma in Eskimos stems from their consumption of large quantities of oily fish, rich in omega-3 fatty acids.[5] Additional impetus for research came from observations that omega-3 fatty acids' possible protective, or even therapeutic, effect might be afforded by their impact on mediators of inflammation thought to be related to the pathogenesis of asthma.[6]

Key Questions

It is from this vantage point that seven questions were investigated in the present systematic review:

1. What is the evidence for the efficacy of omega-3 fatty acids to improve respiratory outcomes among individuals with asthma?
2. What is the evidence that the possible value (efficacy/association) of omega-3 fatty acids in improving respiratory outcomes is dependent on the:
   - Specific type of fatty acid (docosahexaenoic acid [DHA, 22:6 n-3], eicosapentaenoic acid [EPA, 20:5 n-3], docosapentaenoic acid [DPA, 22:5 n-3], alpha linolenic acid [ALA, 18:3 n-3], fish, fish oil)?
   - Specific source (fish, plant, food, dietary supplement [fish oil, plant oil])?

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES • Public Health Service

- Its serving size or dose (fish or dietary supplement)?
- Amount/dose of omega-6 fatty acids given as a cointervention?
- Ratio of omega-6/omega-3 fatty acids used?
- Fatty acid content of blood lipid biomarkers?
- Absolute fatty acid content of the baseline diet?
- Relative fatty acid content of the baseline diet?
- Tissue ratios of fatty acid (omega-6/omega-3) during the investigative period?
- Intervention length?
- Anti-oxidant use?
- The manufacturer and its product(s) purity or presence of other potentially active agents?

3. What is the evidence that, in individuals with asthma, omega-3 fatty acids influence mediators of inflammation which are thought to be related to the pathogenesis of asthma?
4. Are omega-3 fatty acids effective in the primary prevention of asthma?
5. Among individuals with asthma, do omega-3 fatty acids alter the progression of asthma (i.e., secondary prevention)?
6. What is the evidence for adverse events, side effects, or counter-indications associated with omega-3 fatty acid use to treat or prevent asthma (DHA, EPA, DPA, ALA, fish oil, fish)?
7. What is the evidence that omega-3 fatty acids are associated with adverse events in specific subpopulations of asthmatic individual such as diabetics?

Methods

A Technical Expert Panel (TEP) consisting of six members was convened to provide advisory support to the project, including refining the questions and highlighting key variables requiring consideration in the evidence synthesis.

Study Identification

A comprehensive search for citations was conducted using six databases (MEDLINE®, PreMEDLINE®, EMBASE, Cochrane Central Register of Controlled Trials, Commonwealth Agricultural Bureau Health, and Dissertation Abstracts). Searches were not restricted by language of publication, publication type, or study design except with the MeSH® term "dietary fats," which was limited by study design to increase its specificity. Search elements included: scientific terms, with acronyms, as well as generic and trade names relating to the exposure and its sources (e.g., eicosapentaenoic acid; EPA; omega-3 fatty acids; MaxEPA®; fish oil); and, relevant population terms (e.g., asthma; inflammation). Additional published or unpublished literature was sought through manual searches of reference lists of included studies and key review articles, and from the files of content experts. A final set of 1,010 unique references was identified and posted to the UO EPC's Internet-based software system for review.

Studies were considered relevant if they described human populations of any age, involved any type of study design, and investigated the use of any foods or extracts known to contain omega-3 fatty acids as a treatment, primary, or secondary prevention. Populations in treatment or secondary prevention studies had to have received a diagnosis of asthma, whereas those in primary prevention studies could be either at elevated risk for asthma or healthy (i.e., without asthma). Ineligible for treatment studies or secondary prevention studies were populations exclusively exhibiting a subset of the symptoms or signs of asthma (e.g., wheeze), that is, without a clearly stated diagnosis of asthma. In primary prevention studies, methods had to have been employed to identify asthma as well as the omega-3 fatty acids exposure. Studies investigating polyunsaturated fatty acids were included if an explicit evaluation was also made of their omega-3 fatty acid content. Studies where an asthmatic response was experimentally induced in nonasthmatic populations were excluded. A treatment study could assess a respiratory outcome, mediators of inflammation, or safety. A primary prevention study needed to estimate asthma prevalence or incidence, although case-control studies employing outcomes pertinent to this question were also acceptable. A secondary prevention study required a long-term assessment of respiratory function to permit, for example, the observation of a maintained decrement in the need for medication in response to asthma exacerbations.

Two levels of screening for relevance, and two reviewers per level, were employed (bibliographic records, then full articles). Calibration exercises preceded each step of the screening process. Excluded studies were noted as to the reason for their ineligibility using a modified QUOROM format.[7] Disagreements were resolved by forced consensus and, if necessary, third party intervention.

Data Abstraction

Following a calibration exercise, three reviewers independently abstracted the contents of each included study using an electronic Data Abstraction form. A second reviewer checked all abstracted data. Data included the characteristics of the report (e.g., publication status), study (e.g., research design), population (e.g., diagnosis description), intervention/exposure (e.g., omega-3 fatty acid type) and comparator(s) (i.e., comparison group[s]), cointerventions (e.g., asthma medications), withdrawals and dropouts, and outcomes (i.e., respiratory, mediators of inflammation, safety).

After calibration exercises, each study's quality (internal validity) and applicability (external validity) were rated independently by two assessors. Disagreements were resolved by forced consensus and, if necessary, third party intervention. Randomized controlled trials' (RCTs') reporting of

randomization, double blinding, withdrawals and dropouts, and the concealment of allocation, were evaluated using Jadad's[8] and Schulz's validated instruments.[9] Five items selected from Downs and Black's 27-item validated instrument were used to rate the study quality of all other study designs, including a clear description of the study hypothesis or objective, study participants, characteristics of participants lost to followup, the interventions/exposures of interest, and, whether the outcome measures were valid and reliable.[10] One applicability index for treatment and secondary prevention studies, and another for primary prevention studies, were constructed without rigorous validation. Applicability for treatment or secondary prevention studies was defined as the degree to which a given study's sample population was representative of a "typical" North American population of asthmatics. The reference standard for primary prevention studies was the "typical" healthy North American or one at risk for asthma.

Data Synthesis

A summary table provided a question-specific overview of included studies' relevant data presented in greater detail in evidence tables. A question-specific summary matrix situated each study in terms of its quality and applicability ratings. Question-specific qualitative syntheses of the evidence were derived. In consultation with our TEP, forced expiratory volume in one second (FEV_1) was selected as the primary outcome, given its status as a gold standard index of pulmonary function. Problems and limitations of available studies made it inappropriate to conduct meta-analysis of RCT evidence for any question (see Discussion). For the purposes of interpreting the results, a greater emphasis was placed on RCT evidence given its status as the gold standard by which an intervention/exposure's efficacy or effectiveness is investigated.[11]

Results

Literature Search

Of 1,010 records entered into the initial screening for relevance, 851 were excluded. All but five of the remaining 159 reports were then retrieved, and subjected to a more detailed relevance assessment.[12-16] The second relevance screening then excluded 122 reports. In total, 31 reports, describing 26 unique studies, were deemed relevant for the systematic review, with five studies each described by two reports. To simplify matters, only one report per study is referred to in this summary. Yet, data from all of the study documents were included in the qualitative synthesis. Some information regarding the study parameters of an RCT exclusively described by an abstract[17] were taken from a Cochrane review,[18] which had obtained additional details from a source unavailable to the present review team.

Of the included studies, two were abstracts and the rest were published articles in scientific journals. One relevant, published report was identified by manual search. Five reports required translation,[19-23] although one was not translated in time to include its data in the synthesis.[23] Question-specific synopses follow.

Question 1 (Impact on Respiratory Outcomes)

Ten RCTs and nine studies employing other designs (i.e., non-randomized controlled trials [non-RCTs]; noncomparative case series) addressed Question 1. Of the RCTs, two exclusively randomized children,[24,25] one included both older adolescents and adults,[26] one did not report any age data,[27] and six focused on adults.[17,28-32] Two non-RCTs focused on children[22,33] and seven other studies enrolled adults.[19,21,34-38] Of the latter, one was a non-RCT[21] and six involved noncomparative case series.[19,34-38] Given the largely inconsistent picture of efficacy within and across respiratory outcomes, it is impossible to conclude one way or the other whether omega-3 fatty acids are an efficacious adjuvant or monotherapy in improving respiratory outcomes in adults or children. This view is perhaps best illustrated by what was observed with respect to the primary outcome, FEV_1.

Adult RCTs revealed a somewhat contradictory picture of efficacy with respect to FEV_1. One very small adult study (n = 14) that employed uncontrolled dosing of perilla seed oil and corn oil (control) over a short intervention period (n = 4 wk) reported a significant effect. However, two RCTs each observed no benefit relating to an omega-3 fatty acid intervention. One compared high and low doses of EPA ethyl ester[31] over 16 weeks in a small study (n = 12), whereas the second investigated the benefit of low-dose EPA/DHA (versus olive oil) over 10 weeks in the systematic review's highest quality RCT.[32] The latter included one of the largest sample populations (n = 46) included in the evidence review. Emelyanov et al. also demonstrated good control of three confounding factors, while providing one of the most rigorous methods to select its asthma population.[32] No studies of adults using other research designs investigated this outcome. With regard to studies of children, one RCT[25] and a non-RCT[22] observed no benefit in terms of FEV_1. The fact that there were few studies to consider makes the most balanced understanding one that suggests more research is needed before anything definitive can be concluded about the impact of omega-3 fatty acids on FEV_1. A similar picture characterized the other respiratory outcomes.

The inconsistency among study results may be attributable to the heterogeneity in definitions of the:

- Settings (e.g., hospital versus outpatient; countries).
- Populations (e.g., age; gender; clinical picture of asthma, including its severity and concomitants, or triggers with the potential to impact asthma control).
- Interventions and their contrasts with comparators (e.g., different types and amounts of oil and omega-3 fatty acid contents; controlled versus uncontrolled dosing).
- Cointerventions (e.g., asthma medication with varying capacities to control asthma in the short term or long term).

This observation applies to all patterns of results relating to Questions 1, 2, 3, and 4.

Even though study quality, as operationally defined in the present review, was not an obvious shortcoming of the 20 included treatment studies, the very limited generalizability potential for all but two of them[31,36] can be taken to suggest that answering Question 1 requires more research conducted with North American samples. The prominent limitation for the RCTs was limited blinding, and the key limitation for the studies using designs other than an RCT was the poor description of study participants.

Question 2 (Impact of Effect Modifiers)

Given the inappropriateness of conducting meta-analysis, an informal assessment was undertaken looking at the possible consistent or exclusive relationship between significant clinical effects and specific definitions, or levels, of variables with the potential to account for these effects (e.g., high-dose supplementation). These variables are the predefined covariates, as well as any study-defined ones (e.g., type, source, or dose of omega-3 fatty acids). To be eligible, an outcome required results provided by at least two studies, with at least one of them noting a significant clinical effect in favor of the omega-3 fatty acids exposure. Question 2 involved data from 12 of the 19 studies addressing Question 1, including eight RCTs[17,26-32] and four noncomparative case series.[19,35,37,38] None of the studies included children, since the pediatric studies did not meet the criteria established with respect to this question. The assessment did highlight one exposure potentially worth exploring in future empirical investigations of the health effects of omega-3 fatty acids in asthma. It was noted that perilla seed oil supplementation, provided in an uncontrolled fashion to adults, was the only exposure that was exclusively associated with significant clinical effects (12/12) in favor of the omega-3 fatty acids exposure.[28,34,38] Yet, even this observation is likely unreliable. Without the option of meta-analysis, it is difficult to respond adequately to Question 2. It must be concluded that, at present, it is impossible to identify effect modifiers responsible for any significant asthma-related benefits accruing to omega-3 fatty acids supplementation. This exploration was complicated by the fact that few significant effects were found.

Question 3 (Impact on Mediators of Inflammation)

It is likewise unfeasible to conclude one way or the other that omega-3 fatty acids positively influence the lipid mediators of inflammation in adult studies in ways congruent with the biological model implicating the lipoxygenase and cyclooxygenase pathways in asthma. Moreover, virtually no other mediators of inflammation were investigated (e.g., TNF-α).[25] Question 3 was addressed by 11 studies, including five RCTs, one non-RCT, and four noncomparative case series. Of the RCTs, one involved children[25] and four included adults.[26,28,30,31] All of the studies using designs other than an RCT enrolled adults.[19,20,34,36-38]

The only consistent impacts of omega-3 fatty acids on mediators of inflammation involved the suppression of leukotriene C_4[28,34,38] and of polymorphonuclear leukocyte chemotaxis in response to various stimuli.[26,31] However, all of the results must be interpreted with caution given the small sample sizes, as well as the fact that the findings of significant effects for the same outcome involved different intervention-comparator contrasts and varying doses of omega-3 fatty acids. As with the evidence regarding Question 1, considerable clinical heterogeneity characterizes these studies. Their average study quality was good, and their applicability was restricted.

Question 4 (Impact on Primary Prevention)

Six studies investigated Question 4. Of these, one was an RCT looking at the impact of omega-3 fatty acids on neonates[39] and five were observational studies that focused on adults,[40] adolescents,[41] young children and adolescents,[42] and children.[43,44] Dietary fish consumption, including oily fish intake, assessed primarily through a retrospective food-frequency questionnaire, appeared to serve as primary prevention for asthma in two pediatric populations.[43,44] However, asthma prevalence and fish, or oily fish, intake were significantly and positively related in studies that included adolescents from Asia,[41,42] with one of these studies also including some children.[42] In a prospective study of nurses, no association was found between adult asthma onset and dietary fish intake.[40]

Mihrshahi et al.'s factorial RCT is, in large part, a study evaluating the impact of an omega-3 fatty acid regimen (versus placebo), initiated prebirth, on neonates at risk for asthma, given that at least one parent or sibling had received this diagnosis.[39] Their interim results indicated little benefit accruing to the omega-3 fatty acid exposure, yet 18 months is likely too early in life to reliably identify asthma. Final followup at 5 years of age should provide a clearer picture of the value of omega-3 fatty acids as primary prevention. Study quality was better, on average, for the observational studies than for the single RCT; and, as with treatment studies, almost no studies even remotely resembled the North American population standard established in this review.

Question 5 (Impact on Secondary Prevention)

Question 5 could not be addressed since this review failed to identify any secondary prevention studies.

Question 6 (Impact on Safety)

Eight RCTs and two studies employing other designs provided safety data addressing Question 6. No safety profile relating to omega-3 fatty acids as an exposure was observed for primary prevention studies and, on balance, the evidence suggests that the safety profile in the treatment studies was good. Most of the adverse events were related to the capsule delivery of oils, rather than to the oils per se.[17,24,26,29] On several occasions, an inability to swallow capsules led to a withdrawal.

Other participants may have had difficulties taking 18 capsules a day of oil in two specific RCTs, yet these difficulties were not reported.[26,29] The one moderately serious reaction was an undefined number of episodes of nausea and vomiting after ingesting fish oil capsules, and led to a withdrawal.[29] Unspecified numbers of children and adults experienced some (e.g., mild gastrointestinal) discomfort, but not all individuals had been receiving the omega-3 fatty acid exposure.[25] Fishy hiccups or burping were a rare complaint. By far the most serious event linked to a treatment study involved severe apnea associated with repeated allergen challenge.[21] The omega-3 fatty acid exposure had not yet begun.

Question 7 (Impact on Safety in Subpopulations)

Question 7 could not be evaluated since no study reported adverse events associated with a specific subpopulation (e.g., diabetics).

Discussion

Twenty-six studies, described by 31 reports, investigated five of the seven questions posed in this systematic review of the evidence concerning the health effects of omega-3 fatty acids in asthma. The questions of secondary prevention and of safety related to omega-3 fatty acid use in subpopulations of asthmatics could not be addressed due to a lack of studies. Eleven RCTs (ten treatment, one primary prevention) and 15 studies using other designs (ten treatment, five primary prevention) were included. Three of the former and six of the latter involved children or adolescents exclusively. It is likely that, other than Ashida et al.'s noncomparative case series lasting 2 weeks, [38] all treatment studies lasted long enough to demonstrate that a difference could be found in terms of respiratory outcomes and mediators of inflammation. Relevant studies could only be synthesized qualitatively according to the question(s) they addressed.

The present findings suggest that, with omega-3 fatty acid supplementation intended to influence asthma, there is little probability of harm beyond occasional mild discomfort. The most frequent troublesome events were produced by the delivery of the oils in large numbers and sizes of capsules. On the other hand, the lack of sufficiently consistent evidence, as well as a paucity of evidence from well-designed, well-conducted, and adequately powered studies, suggests that no definitive conclusion can yet be drawn regarding the efficacy of omega-3 fatty acid supplementation as a treatment for asthma in children and adults. Likewise, nothing specific can be concluded regarding the role of specific sources, types, or doses of omega-3 fatty acid content in producing significant clinical effects. One possible explanation for the inconsistent findings is the heterogeneity in definitions of settings, populations, interventions/exposures, and the types and doses of asthma medication.

Having too few well-designed studies with which to adequately address this question means that nothing definitive can be said about the influence of omega-3 fatty acids on those mediators of inflammation thought to be implicated in the pathogenesis of asthma, or, about the actual role played by these mediators in asthma. More research is required.

No studies were identified which investigated the potential of omega-3 fatty acids as secondary prevention. Primary prevention attempts were found, yet they lacked unanimity in their findings. While two studies of children outside North America noted a protective effect of dietary fish intake for asthma,[43,44] one American survey, discovered after the present qualitative synthesis was completed, reported no benefit.[45] Moreover, studies outside North America, and primarily including adolescents, found that dietary fish intake actually increased the risk of asthma.[41,42] The only study involving adults found no relationship between these variables.[40] However, many of these studies employed different sampling methods and varying definitions of both the frequency of fish intake and fish types. Likely the most promising attempt to use omega-3 fatty acids as primary prevention involves a large, ongoing RCT of expectant mothers whose children at risk for asthma are being followed for 5 years.[39] To date, 18-month, interim analysis data are too unreliable given the difficulties in diagnosing asthma in children this young.

At this point in time, aside from an acceptable safety profile, it is impossible to definitively conclude anything with respect to the value of using omega-3 fatty acid supplementation in asthma for adults or children either in or beyond North America. Recommendations for future research follow directly from observations of the problems and limitations in the included studies. Flawed or problematic designs need to be avoided in any further attempts to assess the clinical utility of omega-3 fatty acids in asthma. These requirements include better control of factors with the potential to confound the interpretation of results. For example, failing to assure that the delivery of the supplementation is controlled, and hence definable as the "intervention," yields results difficult to interpret. Likewise, failing to assure that there is not an uneven distribution of corticosteroid users or doses across study arms/cohorts can restrict the ability to meaningfully attribute a significant or null effect to the actions of the omega-3 fatty acid supplementation. Asthma medications' capacity to improve asthma symptoms can mask the benefits linked to use of omega-3 fatty acid supplementation.

Poor reporting practices, which led to an inability to know whether, and how, these or other confounders might have influenced individual treatment RCT results, together with the lack of comparability in many of the RCTs' parameters (e.g., intervention-comparator contrasts), led to the decision to forego meta-analysis. Any pooled estimates would have been derived within a context instilling as little confidence in the appropriateness of the extrapolations of results as in the validity of the results themselves.

The present review highlighted some of the methodological issues worth considering in treatment RCTs. As carefully as it

chooses a high quality design, future research likely needs to judiciously select the dose(s), while assuring the identity and purity of the exposure. It should also involve North American samples if there is any belief that omega-3 fatty acid supplementation may be helpful in asthma for North Americans. The need to study this population stems from a paucity of research investigations with this focus; and, possibly because North Americans' high omega-6/omega-3 fatty acid intake ratio may make it less likely that data obtained from populations (e.g., Japanese) with a substantially lower intake ratio (associated with a much higher consumption of omega-3 fatty acids) can be generalized to North Americans.

A potentially interesting hypothesis requiring investigation relates to the possible asthma-related benefits associated with actively and markedly decreasing levels of omega-6 fatty acid intake concurrent with increasing the intake of omega-3 fatty acids. At the same time, given that the present collection of evidence does not constitute the best test of the overarching hypothesis that omega-3 fatty acid supplementation alone can foster asthma-related benefits, more research is likely needed to adequately answer the questions posed in the present systematic review.

Availability of the Full Report

The full evidence report from which this summary was taken was prepared for the Agency for Healthcare Research and Quality (AHRQ) by the University of Ottawa Evidence-based Practice Center, Ottawa, Canada, under Contract No. 290-02-0021. It is expected to be available in March 2004. At that time, printed copies may be obtained free of charge from the AHRQ Publications Clearinghouse by calling 800-358-9295. Requesters should ask for Evidence Report/Technology Assessment No. 91, *Health Effects of Omega-3 Fatty Acids on Asthma*. In addition, Internet users will be able to access the report and this summary online through AHRQ's Web site at www.ahrq.gov.

Suggested Citation

Schachter HM, Reisman J, Tran K, Dales B, Kourad K, Barnes D, Sampson M, Morrison A, Gaboury I, Blackman J. Health Effects of Omega-3 Fatty Acids on Asthma. Summary, Evidence Report/Technology Assessment No. 91. (Prepared by the University of Ottawa Evidence-based Practice Center, Ottawa, Canada.) AHRQ Publication No. 04-E013-1. Rockville, MD: Agency for Healthcare Research and Quality. March 2004.

References

1. National Heart Lung and Blood Institute. Expert Panel Report 2: Guidelines for the diagnosis and management of asthma. NIH Publication No. 97-4051. Bethesda, MD: National Institutes of Health; 1997.
2. Simopoulos AP. The importance of the ratio of omega-6/omega-3 essential fatty acids. Biomed Pharmacother 2002; 56(8):365-79.
3. National Asthma Education and Prevention Program. Expert Panel Report: Guidelines for the Diagnosis and Management of Asthma Update on Selected Topics?2002. J Allergy Clin Immunol 2002; 110(5 Suppl):S141-S219.
4. Global Strategy for Asthma Management and Prevention. National Institutes of Health. National Heart, Lung and Blood Institute. Revised 2002. Updated from: NHLBI/WHO Workshop Report: Global Strategy for Asthma Management and Prevention. Issued January, 1995. NIH Publication No 02-3659. 2002.
5. Horrobin DF. Low prevalences of coronary heart disease (CHD), psoriasis, asthma and rheumatoid arthritis in Eskimos: are they caused by high dietary intake of eicosapentaenoic acid (EPA), a genetic variation of essential fatty acid (EFA) metabolism or a combination of both? Med Hypotheses 1987; 22(4):421-8.
6. Gil A. Polyunsaturated fatty acids and inflammatory diseases. Biomed Pharmacother 2002; 56(8):388-396.
7. Moher D, Cook DJ, Eastwood S, et al. Improving the quality of reports of meta-analyses of randomised controlled trials: the QUOROM statement. Quality of Reporting of Meta-analyses. Lancet 1999; 354(9193):1896-1900.
8. Jadad AR, Moore RA, Carroll D, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin Trials 1996; 17(1):1-12.
9. Schulz KF, Chalmers I, Hayes RJ, et al. Empirical evidence of bias. Dimensions of methodological quality associated with estimates of treatment effects in controlled trials. JAMA 1995; 273(5):408-12.
10. Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. J Epidemiol Community Health 1998; 52(6):377-84.
11. Jadad AR. Randomised controlled trials. London: BMJ Publishing Group; 1998.
12. Romano L. Study on feasibility and results of mid-term dietary supplementation in omega-3 fatty acids [abstract]. 21st European Cystic Fibrosis Conference 1997.
13. Castillo Vizuete JA. ASMA BRONQUIAL SENSIBLE AL ACIDO ACETIL SALICILICO. Dissertation Abstracts International 1988; ume:51-01.
14. Helms PJ. Pathophysiology and prevention of asthma. Annales Nestle [Fr] 2002; 60(2):66-73.
15. Leverve XM, Mustafa I. From specific supports of organ failures to comprehensive understanding of metabolic response. Critical Care and Shock 2003; 6(1):4-6.
16. Palat D, Rudolph D, Rothstein M. A trial of fish oil in asthma. Am Rev Respir Dis 1988; 137(Suppl 4 part 2):328.
17. McDonald C, V. Effect of fish-oil derived omega-3 fatty acid supplements on asthma control. Aust N Z J Med 1990; 20:526.
18. Woods RK, Thien FC, Abramson MJ. Dietary marine fatty acids (fish oil) for asthma in adults and children. [update of Cochrane Database Syst Rev. 2000; (4):CD001283; 11034708]. [Review] [23 refs]. Cochrane Database of Systematic Reviews 2002;(3):CD001283.

19. Hashimoto N, Majima T, Ichimura K, et al. [Effects of eicosapentaenoic acid in patients with bronchial asthma]. Nihon Kyobu Shikkan Gakkai Zasshi 1997; 35(6):634-40.
20. Masuev KA. [The effect of polyunsaturated fatty acids on the biochemical indices of bronchial asthma patients]. Ter Arkh 1997; 69(3):33-5.
21. Masuev KA. [The effect of polyunsaturated fatty acids of the omega-3 class on the late phase of the allergic reaction in bronchial asthma patients]. Ter Arkh 1997; 69(3):31-3.
22. Machura E, Brus R, Kalacinnski W, et al. [The effect of dietary fish oil supplementation on the clinical course of asthma in children]. Pediatr Pol 1996; 71(2):97-102.
23. Sakakibara H, Hirose K, Matsushita K, et al. [Effect of supplementation with eicosapentaenoic acid ethyl ester, MND-21, on generation of leukotrienes by calcium ionophore-activated leukocytes in bronchial asthma]. [Japanese]. Nihon Kyobu Shikkan Gakkai Zasshi 1995; 33(4):395-402.
24. Nagakura T, Matsuda S, Shichijyo K, et al. Dietary supplementation with fish oil rich in omega-3 polyunsaturated fatty acids in children with bronchial asthma. Eur Respir J 2000; 16(5):861-5.
25. Hodge L, Salome CM, Hughes JM, et al. Effect of dietary intake of omega-3 and omega-6 fatty acids on severity of asthma in children. Eur Respir J 1998; 11(2):361-5.
26. Arm JP, Horton CE, Mencia-Huerta JM, et al. Effect of dietary supplementation with fish oil lipids on mild asthma. Thorax 1988; 43(2):84-92.
27. Dry J, Vincent D. Effect of a fish oil diet on asthma: results of a 1-year double-blind study. Int Arch Allergy Appl Immunol 1991; 95(2-3):156-7.
28. Okamoto M, Mitsunobu F, Ashida K, et al. Effects of dietary supplementation with n-3 fatty acids compared with n-6 fatty acids on bronchial asthma. Intern Med 2000; 39(2):107-11.
29. Thien FC, Mencia-Huerta JM, Lee TH. Dietary fish oil effects on seasonal hay fever and asthma in pollen-sensitive subjects. Am Rev Respir Dis 1993; 147(5):1138-43.
30. Stenius-Aarniala B, Aro A, Hakulinen A, et al. Evening primose oil and fish oil are ineffective as supplementary treatment of bronchial asthma. Ann Allergy 1989; 62(6):534-7.
31. Kirsch CM, Payan DG, Wong MY, et al. Effect of eicosapentaenoic acid in asthma. Clin Allergy 1988; 18(2):177-87.
32. Emelyanov AF. Treatment of asthma with lipid extract of New Zealand green-lipped mussel: a randomised clinical trial. Eur Respir J 2002; 20(3):596-600.
33. Gorelova JY, Semikina EM. The changes of lymphocyte membrane receptors in bronchial asthma and atopic dermatitis in pediatric patients receiving treatment with polyenic fatty acids. Z Ernahrungswiss 1998; 37(1):142-3.
34. Okamoto M, Mitsunobu F, Ashida K, et al. Effects of perilla seed oil supplementation on leukotriene generation by leucocytes in patients with asthma associated with lipometabolism. Int Arch Allergy Immunol 2000; 122(2):137-42.
35. Villani F, Comazzi R, De Maria P, et al. Effect of dietary supplementation with polyunsaturated fatty acids on bronchial hyperreactivity in subjects with seasonal asthma. Respiration 1998; 65(4):265-9.
36. Broughton KS, Johnson CS, Pace BK, et al. Reduced asthma symptoms with n-3 fatty acid ingestion are related to 5-series leukotriene production. Am J Clin Nutr 1997; 65(4):1011-7.
37. Picado C, Castillo JA, Schinca N, et al. Effects of a fish oil enriched diet on aspirin intolerant asthmatic patients: a pilot study. Thorax 1988; 43(2):93-7.
38. Ashida K, Mitsunobu F, Mifune T, et al. A pilot study: effects of dietary supplementation with a-linolenic acid-enriched perilla seed oil on bronchial asthma. Allergol Int 1997; 46:181-5.
39. Mihrshahi S, Peat JK, Marks GB, et al. Eighteen-month outcomes of house dust mite avoidance and dietary fatty acid modification in the Childhood Asthma Prevention Study (CAPS). J Allergy Clin Immunol 2003; 111(1):162-8.
40. Troisi RJ, Willett WC, Weiss ST, et al. A prospective study of diet and adult-onset asthma. Am J Respir Crit Care Med 1995; 151(5):1401-8.
41. Huang SL, Lin KC, Pan WH. Dietary factors associated with physician-diagnosed asthma and allergic rhinitis in teenagers: analyses of the first Nutrition and Health Survey in Taiwan. Clin Exp Allergy 2001; 31(2):259-64.
42. Takemura Y, Sakurai Y, Honjo S, et al. The relationship between fish intake and the prevalence of asthma: the Tokorozawa childhood asthma and pollinosis study. Prev Med 2002; 34(2):221-5.
43. Hodge L, Salome CM, Peat JK. Consumption of oily fish and childhood asthma risk.
44. Satomi H, Minowa M, Hatano S, et al. An epidemiological study of the preventive effect of dietary fish on bronchial asthma. Koshu Eisei In Kenkyu Hokoku 1994; 43(3):305-14.
45. Schwartz J, Gold D, Dockery DW, et al. Predictors of asthma and persistent wheeze in a national sample of children in the United States. Association with social class, perinatal events, and race. Am Rev Respir Dis 1990; 142(3):555-62.

www.ahrq.gov
AHRQ Pub. No. 04-E013-1
March 2004

ISSN 1530-440X